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THE ESSENTIAL OIL OF *PHYLLOCLADUS TRICHOMANOIDES*

LINDSAY H. BRIGGS AND MAURICE D. SUTHERLAND

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The genus *Phyllocladus* is a small one of six species, three being endemic to New Zealand, one to Tasmania, another to Borneo, while the final species is distributed in New Guinea and the Philippine Islands. The Tasmanian species, *P. rhomboidalis*, contains an essential oil shown by Baker and Smith (1) to contain *l*- α -pinene, an unidentified sesquiterpene and the diterpene, phyllocladene. A small specimen of the winter oil of *P. alpinus* appeared to be mainly phyllocladene (Briggs, 2) but a larger sample examined by Brandt (3) contained unidentified terpene and sesquiterpene constituents in addition.

An examination of the winter and summer essential oils of *P. trichomanoides* has now been made, six constituents being isolated from the winter oil, while seven constituents have been identified from the summer oil, which contains other unidentified compounds in small amount. The work was commenced in 1937 but through various circumstances had to be discontinued for some years with consequent loss of material because fractions for later examination had to be repeatedly distilled to free them from oxidized or polymerized products.

Samples of oil collected at various times of the year showed some variation of the physical constants, a variation which was more marked in a detailed study of the constituents of the winter and summer oils.

The winter oil, obtained in 0.20% yield, had d_{16} 0.9031, n_D^{25} 1.4855, $[\alpha]_D^{25} +16.29^\circ$; the acid and saponification number and the saponification number after acetylation showed the presence of only traces of acids, esters or alcohols while aldehydes and phenols were absent. The oil was repeatedly fractionated with a Widmer column, the hydrocarbon fractions over sodium-potassium alloy, the terpene section at atmospheric pressure, and the higher fractions *in vacuo*. The results of the main fractionation are recorded in Table I.

α -Pinene and dipentene were identified through known derivatives while two sesquiterpene fractions were obtained neither of which was identified. One, b.p. 110–114°/10 mm., d_{25} 0.9189, n_D^{25} 1.4928, $[\alpha]_D +20.0^\circ$, $[R_L]_D$ 64.69, gave a crystalline nitrosite, m.p. 92.5–94°, not recorded from any other sesquiterpene, and cadalene on dehydrogenation. These facts, and its physical constants, suggest that it is a new tricyclic sesquiterpene, from which ozonization failed to yield any well characterized product. This constituent does not appear to be present in the summer oil; $[\alpha]_D^{25} +5.66^\circ$.

The second sesquiterpene, b.p. 122–127°/10 mm., d_{25} 0.9158, n_D^{25} 1.5038, $[R_L]_D$ 65.89, has physical constants of a dicyclic sesquiterpene, possibly identical with calamene for which the following constants are recorded: b.p. 123–126°/10.5 mm., d_{19}^{20} 0.9224, n_D^{20} 1.50572 (4). Like calamene it affords cadalene on dehydrogenation with palladized charcoal but, on the other hand, cadinene dihydrochloride by the action of hydrogen chloride, a derivative not obtained from

calamene. It may, however, be an impure cadinene which was definitely identified from the summer oil (*q. v.*). Ozonization failed to yield any well characterized product.

Crystals separated from the last high-boiling fractions on long standing, and were shown to be a mixture of the diterpenes, phyllocladene, and isophyllocladene, with a third unknown constituent.

The summer oil obtained in 0.13% yield had $d_{25} 0.8876$, $n_D^{25} 1.4839$, $[\alpha]_D^{20} +8.48^\circ$, acid number 1.1, saponification number 3.7, saponification number after acetylation 9.2. Distillation was carried out at 10 mm. using a Widmer column with a 10:1 reflux ratio for the earlier fractionations, and a Bower and Cooke type

TABLE I
DISTILLATION OF WINTER OIL

FRACTION	B. P., C°	PRESSURE, MM.	n_D^{15}	WEIGHT, G.	FRACTION %
1	154	752	1.4592	7.57	1.9
2	154	"	1.4550-1.4567	70.97	17.7
3	154-155	"	1.4567-1.4570	26.90	6.7
4	155-156	"	1.4570-1.4575	21.29	5.3
5	50	8	1.4625	12.93	3.2
6	50-80	"	1.4772	7.82	2.0
7	80-103	"	1.4870	8.82	2.2
8	103-110	"	1.4874	38.31	9.6
9	110-120	9	1.4913	79.19	19.8
10	120-130	"	1.4977	24.22	6.1
11	130-180	"	1.5054	21.34	5.3
12	180-185	"	1.5109	46.51	11.6
13	ca. 165	3	1.5148	5.73	1.4
14	Residue			14.22	3.6
	Loss			14.18	3.5
				400.00	

column (5) for the later sesquiterpene fractions; the results of the main fractionation are recorded in Table II. Only those fractions were examined whose physical constants indicated reasonable homogeneity.

The constants of fraction A1 corresponded to those of α -pinene the presence of which was confirmed by oxidation to pinonic acid according to Delépine (6). In agreement with the rotation $+17.79^\circ$, both the active and *dl* forms were isolated.

Refractionation of A2 and A3 produced further quantities of α -pinene, together with a small fraction, with constants approximating those of myrcene. Treatment of this fraction with maleic anhydride furnished the adduct of myrcene, and the corresponding dicarboxylic acid after saponification, thus establishing its presence.

From the refractionation of A4 and the forerunnings from the redistillation of A5, small fractions of high-boiling terpenes were obtained. Addition of bromine

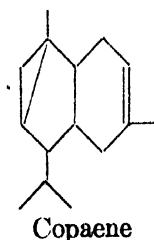
in amyl alcohol-ether to the first of these gave a tetrabromide, m.p. 125.5–126.5°, crystallizing from ethyl acetate in clusters of plates and thus agreeing with γ -terpinene tetrabromide, which has the melting point 128° (7) and crystallizes in the same manner. This was confirmed by the permanganate oxidation of the next fraction, which gave a product, m.p. 235°, which is the m.p. recorded for *p*-menthane-1,2,4,5-tetrol similarly obtained from γ -terpinene (8).

The physical constants of a sesquiterpene obtained by refractionation of A5 agree with those of copaene, whose identity is rigidly confirmed by the following reactions. The hydrogenation value corresponded to the presence of 87% of tricyclic sesquiterpene which gave cadinene dihydrochloride by the action of hydrogen chloride in ether, and cadalene, characterized through the picrate, on

TABLE II
DISTILLATION OF SUMMER OIL

FRACTION	B.P. /10 MM., °C	n_D^{25}		d_{25}	$[\alpha]_D^{25}$	WEIGHT, G.
		1st Drop	Main Fraction			
A 1	37–39	1.4618	1.4618	0.8506	+17.79	22.9
A 2	39–44	1.4619	1.4629	.8447	+16.59	52.4
A 3	45–49	1.4640	1.4668	.8069	+11.99	10.4
A 4	50–100	1.4702	1.4773	.8875	+18.39	4.0
A 5	100–113	1.4800	1.4882	.9078	–0.99	22.8
A 6	112–120	1.4895	1.4939	.9069	–8.71	16.0
A 7	124–129	1.5008	1.5033	.9220	–2.34	19.0
A 8	131/5 mm.	1.5030	– 1.5065	very viscous—added to residue		
A 9	Residue	Solidified on standing				27.0
	Loss					1.5
						176.0

dehydrogenation with palladium-charcoal. Oxidation with potassium permanganate afforded copaene ketonic acid, characterized as the semicarbazone, and as the semicarbazone of its methyl ester; the melting points agreed with those recorded by Semmler and Stenzel (9). The copaene from this oil has been used for degradative purposes, and the constitution has now been shown to be (10)



The forepart of fraction A6 also consisted mainly of copaene.

From the refractionation of A7 two small dicyclic sesquiterpene fractions were obtained, both of which gave cadinene dihydrochloride by the action of hydrogen

chloride, while cadalene, as the picrate, could also be obtained from the second fraction by dehydrogenation with palladized charcoal. Since both fractions had constants agreeing with those of cadinene, the presence of this constituent is confirmed.

The residue in the main distillation partly solidified on standing. After separation of the solid, the residual oil was repeatedly distilled systematically, filtering off any solid separating on cooling. Finally a fraction was obtained, b.p. 134–137°/5 mm., n_D^{25} 1.5040, d_{25} 0.9674, $[\alpha]_D -9.5^\circ$ in chloroform. The molecular refraction 67.92, agreed with that of a bicyclic sesquiterpene alcohol (calculated for $C_{15}H_{26}O$, $[\bar{r}]_2$ 68.07). It failed to give a crystalline acid phthalate or 3,5-dinitrobenzoate and is therefore probably tertiary. Hydrogen chloride in acetic acid, but not in dry ether, yielded *l*-cadinene dihydrochloride, undepressed by an authentic specimen, indicating its carbon framework. The constants do not agree well with any of the known cadinols.

The residual solid from the first distillation after repeated crystallization from alcohol and ethyl acetate melted at 94–95°, and its identity with phyllocladene was confirmed by mixed melting point, and isomerization with alcoholic sulfuric acid to isophyllocladene.

Further systematic crystallization of the mother liquors from which phyllocladene separated was carried out using ethyl acetate, and afforded isophyllocladene, m.p. 108–110°, identified by mixed melting point and conversion to α -dihydrophyllocladene. This is the first record of the occurrence of both phyllocladene and isophyllocladene in an essential oil, but this has since been observed also in the oil of *Araucaria excelsa* (11).

Still further investigation of the mother liquors gave 50 mg. of material, m.p. 68–83°, obviously still impure but with $[\alpha]_D +41^\circ$, a higher rotation than either phyllocladene or isophyllocladene, indicating another compound of this range.

Finally, by distillation of the liquid diterpene residues, nearly 5 grams of an apparently homogeneous tetracyclic diterpene was obtained, which failed, however, to give crystalline products on attempted isomerization with alcoholic sulfuric acid, dehydrogenation with palladized charcoal, or oxidation with permanganate.

EXPERIMENTAL

A. The Winter Oil

The leaves and terminal branchlets of *Phyllocladus trichomanoides* growing near Auckland were collected in May and steam distilled the next day in two batches with an average yield of 0.20%.

The physical and chemical constants already enumerated were determined by standard methods. The oil was then systematically fractionated through jacketed Widmer columns with an electrically controlled manostat, the results of the first fractionation being recorded in Table I. The records of the various refractionations are omitted but the details of the relatively homogeneous fractions obtained are included in the following.

α -Pinene Refractionation of fractions 1–4 failed to yield any component other than α -pinene, the main fraction having b.p. 154–154.5°/765 mm. (from sodium), n_D^{25} 1.4633,

d_{25} 0.8522, $[\alpha]_D^{12} +19.35^\circ$. Its identity with α -pinene was proved by preparation of the nitrosochloride, m.p. 110–112°, undepressed by an authentic specimen (12), the nitrolbenzylamine, m.p. 123–124° (lit. m.p. 122–123°) and the nitrolpiperide, m.p. 118–118.5° (lit. m.p. 118–119°).

Dipentene. Refractionation of fraction 5 gave a small fraction, b.p. 158–162°/766 mm., n_D^{12} 1.4727, which in the light of the results from the summer oil (*q. v.*) could well be myrcene, and a further fraction, b.p. 170–172°, n_D^{12} 1.4770, identified with dipentene by the preparation of the tetrabromide, m.p. 123–124° from ethyl acetate (lit. m.p. 125–126°). The small amount of dipentene probably arises in this case from the α -pinene by isomerization under the influence of heat during the protracted fractionation (13).

Sesquiterpenes. (a) In the subsequent series of fractionations under reduced pressure a sodium-potassium alloy was employed, leading to the almost complete removal of the small amounts of oxygenated constituents. Of the two sesquiterpenes isolated, the first had b.p. 111–112°/10 mm., d_{25} 0.9144, n_D^{25} 1.4912, $[R_L]_D$ 64.65. After standing for some years this fraction had oxidized considerably but after repeated distillation from sodium and refractionation it showed but slight change in its constants *viz.* b.p. 110–114°/10 mm., d_{25} 0.9189, n_D^{25} 1.4928, $[\alpha]_D +20.0^\circ$, $[R_L]_D$ 64.49, indicating a tricyclic sesquiterpene, (calculated for $C_{15}H_{24}$ $[\overline{R_L}]_D$ 64.40).

When bromine vapor was added to a solution of the original fraction in glacial acetic acid a bluish green color was produced passing to greenish blue on standing and disappearing on shaking; on heating it turned to indigo blue. Concentrated sulfuric acid gave a brownish lower layer with a pink-red coloration above.

A crystalline nitrosite could be prepared from the original fraction by passing nitrous fumes (prepared by the action of concentrated sulfuric acid on sodium nitrite) through an ethereal solution of the sesquiterpene cooled in a freezing mixture, the solution first turning blue-green, then dark green, and finally brown. The colorless crystals formed had m.p. 92.5–94°, unchanged by recrystallization from ether. Despite the fact that the same derivative was also prepared in alcohol-acetic acid solution (2:1) to which a little ether was also added to effect homogeneity, it could not be obtained from the later repurified material.

The sesquiterpene did not form a solid hydrochloride or nitrosochloride.

A mixture of the sesquiterpene (750 mg.) and palladized charcoal (80 mg.) was boiled for 4 hours. The picrate from the product, after repeated crystallization from absolute alcohol formed orange-red needles, m.p. 114–115°, undepressed by an authentic specimen of cadalene picrate (14).

(b) The second sesquiterpene isolated had b.p. 124–127°/10 mm., d_{25} 0.9149, n_D^{25} 1.5053 $[R_L]_D$ 66.17. The same fraction purified some years later had b.p. 122–127°/10 mm., d_{25} 0.9158, n_D^{25} 1.5038, $[\alpha]_D^{25} +5.6^\circ$, $[R_L]_D$ 65.89, constants with little change and which indicated a bicyclic hydrocarbon (calculated for $C_{15}H_{24}$ $[\overline{R_L}]_D$ 66.14).

The following color reactions were produced in a solution of the oil in glacial acetic acid: concentrated sulfuric acid—crimson; concentrated hydrochloric acid—light crimson; phosphoric acid—madder-rose at the interface; bromine vapor—crimson changing to blue as it passed down the solution.

The sesquiterpene (1.22 g.) was dehydrogenated by heating with palladized charcoal (100 mg.) for 4 hours. Picric acid added to the blue oil on the water-bath formed brown needles, which after recrystallization from alcohol had m.p. 114–116°, undepressed by an authentic sample of cadalene picrate (yield 25%) (15).

When dry hydrogen chloride was passed through an ethereal solution of the sesquiterpene in a freezing mixture, the solution remained colorless for about 10 minutes and then suddenly turned dark red with evolution of excess acid fumes shortly afterwards. After standing in the ice-chest overnight the ether was removed from the reddish-blue oil, which crystallized on addition of glacial acetic acid and cooling. The colorless needles, after recrystallization from alcohol, had m.p. 115–117°, undepressed by *l*-cadinene dihydrochloride (yield 3%) (15).

From the highest-boiling fractions crystals separated on long standing, m.p. 86.5–87.5° after recrystallization from alcohol. Repeated crystallization from alcohol and methyl alcohol raised the melting point to 92°, at which stage the melting point was raised to 93–95° by phyllocladene and to 94.5–104.5° by isophyllocladene. The material of m.p. 92° is thus a mixture of phyllocladene and isophyllocladene [compare the mixed melting point curve for these isomers (Briggs and Taylor, 11) and their isolation from the summer oil]. Since the eutectic of the phyllocladene-isophyllocladene mixture is 90°, the melting point of the original mixture, 86.5–87.5°, indicates admixture with a third unknown solid component. The total quantity, however, was too small for further investigation.

B. The Summer Oil

This was obtained in November from trees of the Waipoua Forest, supplied through courtesy of the State Forest Service to whom we express our sincere thanks. The leaves were steam distilled in the usual way and when the distillation was finished, steam was passed through the empty condenser to remove a small quantity of the diterpene phyllocladene which had crystallized out.

The results of the preliminary distillation carried out with a 50-cm. Widmer column and a 10:1 reflux ratio are recorded in Table II. Later distillations, particularly of the higher fractions, were effected through a three-foot Bower and Cooke type column (5). Only the constants of the relatively homogeneous fractions so obtained are recorded in the following text.

α -Pinene. By refractionation of fractions A1–A3 a main cut was obtained, b.p. 39–39.5°/10 mm., d_{20}^4 0.8512, n_D^{20} 1.4621, $[\alpha]_D^{20} +21.03^\circ$ agreeing with the constants of specially purified α -pinene by Fuguitt, Stallcup, and Hawkins (16). Oxidation according to Delépine (6) furnished pinonic acid, b.p. 159°/5 mm., from which the *cis-dl*-acid, m.p. 104–105°, could be obtained by repeated crystallization from benzene. The low-melting product from the mother liquors was converted to the oxime, and the optically active β -form of pinonic acid oxime crystallized from methyl alcohol in needles, m.p. 123–125° (lit. m.p. 128°).

Myrcene. Refractionation of A3 afforded 3.3 g. of an oil having b.p. 40–50°/10 mm., d_{20}^4 0.8060, n_D^{20} 1.4660, $[\alpha]_D^{20} +7.76^\circ$. An exothermic reaction occurred on warming a mixture of this fraction (1 g.) with maleic anhydride (1 g.). The distilled product, 0.85 g., b.p. 178°/5 mm., solidified on cooling. The crystals obtained on recrystallization from light petroleum had m.p. 34–35°, with zero rotation. The dicarboxylic acid obtained after saponification was recrystallized from aqueous alcohol and acetonitrile and then melted at 123–123.5°. Diels and Alder (17) record m.p.s. of 34–35° and 122–123° for these respective compounds.

γ -Terpinene. This was identified from a fraction, b.p. 58–62.5°/10 mm., d_{20}^4 0.8361, n_D^{20} 1.4696, $[\alpha]_D^{20} +36.0^\circ$, 0.6 g., obtained by refractionation of A4 and the forerunnings from the refractionation of A5. Bromine (1.25 g.) in ethereal solution was added to a solution of the fraction (0.53 g.) in amyl alcohol (0.6 cc.) and ether (1.2 cc.) in a freezing mixture. The crystalline precipitate which formed overnight, after repeated crystallization from ethyl acetate, produced clusters of plates, m.p. 125.5–125.6°. Richter and Wolff (7) record m.p. 128° for γ -terpinene tetrabromide. Dipentene tetrabromide of similar melting point crystallizes from ethyl acetate in needles and considerably depressed the melting point of the above product.

Further evidence for the presence of γ -terpinene was afforded by oxidation of the next fraction, similarly obtained, which had b.p. 63–80°/10 mm., d_{20}^4 0.8530, n_D^{20} 1.4796, $[\alpha]_D^{20} +14.1^\circ$ (0.7 g.). A suspension of this fraction (440 mg.) in an aqueous solution of potassium hydroxide (100 mg. in 50 cc.) was mechanically shaken for three hours, potassium permanganate (680 mg.) being added in four equal portions at half-hourly intervals. The precipitated manganese dioxide was extracted three times with boiling water, the combined filtrates saturated with carbon dioxide and evaporated to dryness. The brown oil so obtained deposited 5 mg. of colorless crystals, m.p. ca. 235°, after standing in aqueous alcoholic solution. Wallach (8) obtained *p*-menthane-1,2,4,5-tetrol, m.p. 237°, from a similar oxidation of γ -terpinene.

Copaene. The main fraction (6.67 g.) obtained on redistillation of A5 had b.p. 112.5–114.5°/10 mm., d_{25}^4 0.9061, n_D^{25} 1.4877, $[\alpha]_D^{25}$ +0.19°, $[R_L]_D$ 64.84. Catalytic hydrogenation on a semi-micro scale using Adams' catalyst and glacial acetic acid as solvent gave the double bond content as 1.13 ± 0.03 indicating a mixture of 87% tricyclic sesquiterpene and 13% bicyclic.

A mixture of this fraction (850 mg.) with palladized charcoal (100 mg.) was boiled under reflux for 9 hours. The crude picrate of the product, prepared in methyl alcohol, was filtered, the hydrocarbon regenerated and then treated with the calculated quantity of picric acid. The picrate, after crystallization from alcohol, had m.p. 114–115°, undepressed by an authentic specimen of cadalene picrate.

Dry hydrogen chloride was passed into an ethereal solution of the same fraction in a freezing mixture. After standing for some days in the refrigerator, two crops of crystals were obtained, (a) m.p. 110–115° (160 mg.), and (b) m.p. 70–75° (250 mg.). The first product, after repeated crystallization from alcohol had $[\alpha]_D -38^\circ \pm 2^\circ$ in chloroform and m.p. 117–117.5°, undepressed by *l*-cadinene dihydrochloride. The second crop after repeated crystallization from methyl alcohol formed plates m.p. 85–86°, but was unfortunately lost before analysis.

A suspension of this fraction (2.04 g.) in ice and water (40 g.) containing potassium permanganate (3.6 g.) and ammonium sulfate (1.55 g.) was shaken mechanically for 2 hours. The manganese dioxide was dissolved by passage of sulfur dioxide and the organic matter extracted with chloroform. Distillation afforded a main fraction, b.p. 155–175°/0.5 mm., 0.9 g., partly soluble in sodium hydroxide solution. Sodium carbonate solution added to its ethereal solution removed the acid (0.5 g.), recovered by acidification. The semicarbazone separated in warty masses on allowing the acid (250 mg.) to react with semicarbazide hydrochloride in dry pyridine overnight. After repeated crystallization from alcohol, clusters of colorless needles separated, m.p. 222°. Semmler and Stenzel (9) record m.p. 221° for the semicarbazone of copaene ketonic acid.

Anal. Calc'd for $C_{15}H_{27}N_3O_2$: C, 62.10; H, 8.80.

Found: C, 62.34; H, 8.70.

The methyl ester was prepared as a pale yellow oil by the interaction of excess diazomethane with the acid (250 mg., dried at 100° over P_2O_5 for 2 hours) in dry ethereal solution. The semicarbazone, prepared as above, separated from aqueous methyl alcohol in needles, m.p. 194–196°, $[\alpha]_D +25^\circ \pm 3^\circ$ ($l = 1$, $c = 0.37$ in methyl alcohol). Semmler and Stenzel (9) found $[\alpha]_D +27^\circ$ for this ester and m.p. 193–194° for its semicarbazone.

Cadinene. Refractionation of the higher-boiling sesquiterpene portions gave two similar fractions, (a) b.p. 128–130°/10 mm., d_{25}^4 0.9149, n_D^{25} 1.5041, $[\alpha]_D -15.8^\circ$, 1.11 g., and (b) b.p. 130–131°/10 mm., d_{25}^4 0.9170, n_D^{25} 1.5058, $[\alpha]_D -9.4^\circ$, 1.09 g.

The first fraction (580 mg.) in dry ethereal solution was saturated with dry hydrogen chloride in a freezing mixture. The red solution deposited no crystalline material on standing, but the residue, after removal of the ether and acid, crystallized on standing in the refrigerator. Recrystallization from alcohol afforded colorless needles, m.p. 116.5–118°, undepressed by pure *l*-cadinene dihydrochloride. The second fraction yielded the same derivative.

Dehydrogenation of the second fraction (550 mg.) with palladized charcoal in a stream of carbon dioxide yielded cadalene, isolated as its picrate (40 mg.), m.p. 113–115° after crystallization from alcohol; undepressed by an authentic specimen.

Sesquiterpene alcohol. From the final liquid portions of the oil from which the solid diterpenes had separated, repeated fractionation yielded a fairly homogeneous sesquiterpene alcohol, 1.8 g., b.p. 134–137°/5 mm., d_{25}^4 0.9674, n_D^{25} 1.5040, $[\alpha]_D -9.5^\circ$ ($l = 1$, $c = 2.21$ in chloroform), $[R_L]_D$ 67.92, (calculated for $C_{15}H_{26}O$ $\sqrt{2}$ 68.07).

Dry hydrogen chloride was passed through a solution of the alcohol (200 mg.) in glacial acetic acid kept in a freezing mixture. The crystals separating from the blue liquid, after recrystallization from alcohol, had m.p. 117–118°, undepressed by *l*-cadinene dihydrochloride.

Phyllocladene. The solid residues from fractions A8 and A9, after repeated crystallization from alcohol, had $[\alpha]_D +16.5^\circ$ ($l = 1$, $c = 13.15$ in chloroform) and m.p. $94-95^\circ$, undepressed by pure phyllocladene.

The product, after isomerization in alcoholic sulfuric acid, crystallized from ethyl acetate in needles, $[\alpha]_D +23.4^\circ$ ($l = 1$, $c = 2.06$ in chloroform), m.p. $109-111^\circ$. Briggs (18) records $[\alpha]_D^{25} +15.8^\circ$ for phyllocladene and $[\alpha]_D +23.4^\circ$ for isophyllocladene.

Isophyllocladene. The solid separating from the phyllocladene mother liquors was repeatedly crystallized from alcohol and ethyl acetate and finally formed needles, $[\alpha]_D +22.2^\circ$ ($l = 1$, $c = 4.06$ in chloroform), m.p. $108-110^\circ$, undepressed by pure isophyllocladene (yield ca. 1 g.).

The dihydro derivative, prepared in glacial acetic acid with Adams' catalyst, formed needles (not plates as recorded in the literature) from methyl alcohol, m.p. $72-72.5^\circ$, undepressed by pure α -dihydrophyllocladene (18).

Solid diterpene. Still further working up of the solid diterpene mixture afforded small quantities (ca. 50 mg.) of low-melting material, usually with m.p. ca. $70-80^\circ$, and with rotations higher than that of either phyllocladene or its isomeride, the highest rotation found being $[\alpha]_D +41^\circ$. Attempted purification by chromatographing on alumina effected only a partial separation. Isomerization of one such fraction with alcoholic sulfuric acid furnished a product, m.p. $108-110^\circ$ from ethyl acetate, obviously isophyllocladene.

Since the eutectic of phyllocladene and isophyllocladene is 90° (11) the low-melting material must contain a third solid component but the amount available was too small for further investigation.

Liquid diterpene. Final distillation of the liquid diterpene residues yielded 4.96 grams of an apparently homogeneous colorless constituent, b.p. $156-157^\circ/1$ mm., $d_{25} 0.9640$, $n_D^{25} 1.5168$, $[\alpha]_D +22.6^\circ$, $[R]_D^{25} 85.36$ (calculated for $C_{20}H_{32}$ $[\overline{M}] 85.29$), from which no solid derivatives could be obtained.

All melting points are uncorrected.

The analyses are by J. Mills, Adelaide University.

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SUMMARY

The essential oil from the leaves of *Phyllocladus trichomanoides* has been shown to contain the following constituents. The winter oil: α -pinene, dipentene, a possibly new tricyclic sesquiterpene, a second sesquiterpene (possibly calamene or cadinene), phyllocladene, and isophyllocladene.

The summer oil: α -pinene, myrcene, γ -terpinene, copaene, cadinene, a cadinol, phyllocladene, isophyllocladene, and an unidentified solid and liquid diterpene.

AUCKLAND, NEW ZEALAND

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STUDIES ON THE CONVERSION OF ERGOSTEROL TO ADRENAL CORTICAL HORMONES¹

WERNER BERGMANN AND PHILIP G. STEVENS²

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In 1942 investigations were begun in this laboratory which aimed at a partial synthesis of adrenal cortical hormones from ergosterol (Ia). At that time this sterol appeared to be an attractive starting material because of the comparative ease with which it may be converted to derivatives like dehydroergosterol (IIa) (1) which possess unsaturation at C-11 and which might therefore lend themselves to the introduction of oxygen at this point. In addition the 22,23-double bond was expected to facilitate removal of the side chain to permit its replacement by one of the typical side chains of adrenal cortical hormones. Finally the 5,6-double bond, in case it could be retained during the contemplated series of reactions, should simplify the conversion of one of the final products to the 4,5-unsaturated ketone.

The present paper deals with some of the earlier exploratory steps taken towards the possible solution of the problem. The first concerned itself with the degradation of the side chain of ergosterol (Ia) under conditions which left intact the system of conjugated double bonds in ring B, which was to serve as a starting point for further alterations of the molecule. To protect this system, ergosteryl acetate (Ib) was converted into its maleic anhydride addition product by the method of Inhoffen (2). The adduct (III) was then subjected to various types of oxidation in an effort to bring about complete elimination of the side chain. When these attempts met with little tangible success, the action of ozone upon the adduct was investigated. Substantial attack of this reagent upon the 6,7-double bond of the adduct was not anticipated, since its relative inertness had already been demonstrated by Inhoffen (2), and since it was shown in this laboratory that even in the presence of a large excess of perbenzoic acid the adduct reacts to give only the 22,23-epoxide (IV).

Ozonization of the adduct (III) gave a satisfactory yield of solid material which at first was immediately oxidized to an acid which was isolated in the form of its methyl ester, m.p. 272°; $[\alpha]_D^{25} - 10.8^\circ$. The observed analytical values for this derivative, and the fact that it gave off maleic anhydride upon heating, suggested its identity with the maleic anhydride adduct of methyl 3(β)-acetoxybisnor-5,7-choladienate (VI b). This was substantiated by the hydrolysis of the acid (VI a) to the tricarboxylic acid (VII a) and the conversion of the latter to the trimethyl ester (VII b), m.p. 184–185°; $[\alpha]_D^{25} - 30^\circ$, and reconversion to the 3(β)-acetoxy-monocarboxylic acid (VI a), m.p. 260°. Heating of the methyl ester (VI b) *in*

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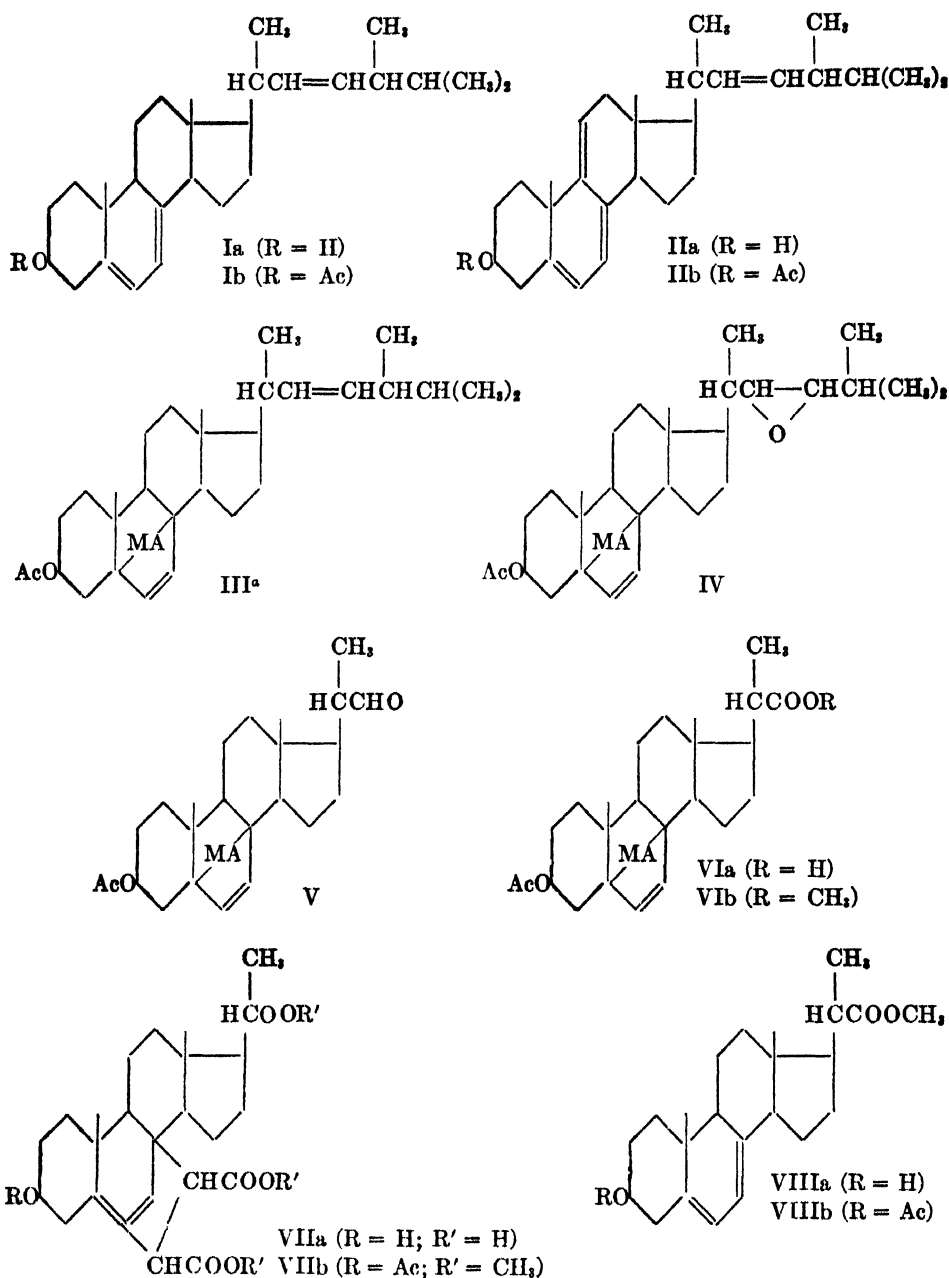
² Present address: General Aniline and Film Corporation, Park Avenue, New York.

vacuo afforded maleic anhydride and an oil from which the desired methyl 3(β)-acetoxybisor-5,7-choladienate (VIII b), m.p. 147°; $[\alpha]_D^{25} - 83^\circ$, was eventually obtained in a yield of thirty per cent. The new ester shows the typical absorption spectrum of 5:6,7:8-unsaturated steroids, and its observed rotation agrees well within the limits of experimental error with the value calculated on the basis of Barton's method of comparing molecular rotation differences (3). Like the esters of other bisnoracids, the present ester is difficult to hydrolyze and reacts with alkali under moderate conditions only with hydrolysis of the 3(β)-acetoxy group to afford methyl 3(β)-hydroxybisor-5,7-choladienate (VIII a), m.p. 163–165°; $[\alpha]_D^{25} - 120^\circ$. Catalytic hydrogenation of the ester (VIII b) in a neutral medium gives a dihydro derivative, m.p. 136°; $[\alpha]_D^{25} - 4.2^\circ$, which according to the work of Wieland (4) and Barton (3) is to be formulated as methyl 3(β)-acetoxybisor-7-cholenate (IX).

In subsequent studies it was observed that reduction of the ozonide of the adduct (III) afforded in a yield of seventy-five per cent the nicely crystalline aldehyde (V), m.p. 206–208°; $[\alpha]_D^{25} - 16.4^\circ$. The identity of the aldehyde was established through the ready formation of a 2,4-dinitrophenylhydrazone, m.p. 246°. Later investigations, to be published elsewhere, have shown that by analogous methods other sterols, unsaturated in the side chain, may also be converted in good yields into the aldehydes, which should prove to be valuable intermediates in the partial synthesis of sterols with diverse side chains. Because of its greater reactivity, the aldehyde (V) is a more suitable intermediate for a further degradation of the side chain than the methyl ester (VIII b). It was at first attempted to convert the aldehyde (V) into the methyl ketone (XIII) by way of α -bromination, replacement of the bromine by hydroxyl, and oxidation of the ensuing hydroxy aldehyde. The first step in the contemplated series of reactions proved successful, and there was obtained a nicely crystalline monobromide (X), m.p. 180°. Difficulties, however, were encountered in completing the contemplated conversion. Further investigations along these lines were eventually temporarily discontinued in favor of a more promising approach based on the degradation of the enol acetate of the aldehyde. This derivative (XI or XII), m.p. 189–190°, is readily obtained by heating the aldehyde (V) with acetic anhydride in a sealed tube. It was expected that ozonolysis of this derivative would yield the desired methyl ketone (XIII). The actual reaction product, m.p. 287°, gave analytical data contra-indicating its identity with the expected product (XIII), and in agreement with those calculated for the 17-ketone (XIV). Unfortunately the splitting of the adduct, a prerequisite for the final proof of its structure has not yet given identifiable products, with the exception of some maleic anhydride. If subsequent studies should prove structure XIV to be that of the product of ozonolysis, it must be assumed that the acetylation of the aldehyde (V) is accompanied by a migration of a double bond to afford the diacetate (XII). An analogous sequence of reactions is now being studied in this laboratory on sterols, unsaturated in the side chain, which do not require protection by maleic anhydride.

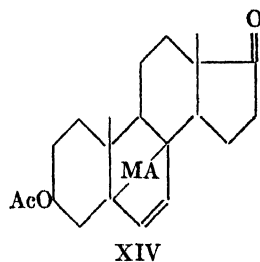
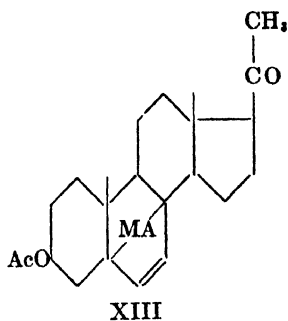
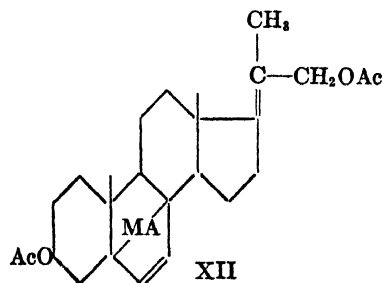
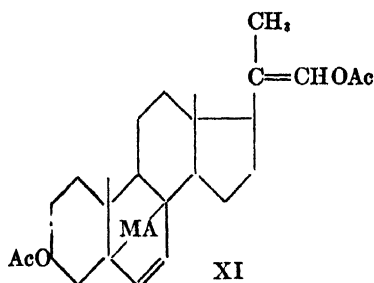
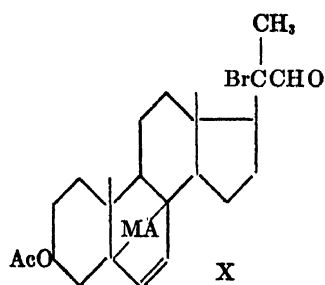
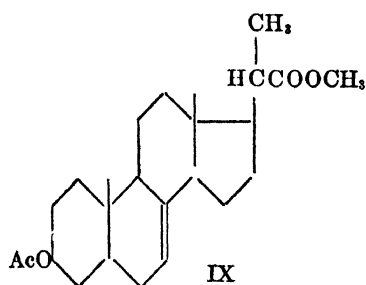
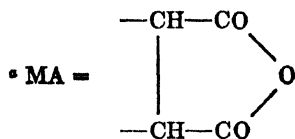
The next exploratory step in the direction of a partial synthesis of adrenal cor-

tical hormones from ergosterol dealt with the preferential addition of oxygen to the 9,11-double bond of dehydroergosteryl acetate (II b), and the degradation



of the side chain of the resulting product. Dehydroergosteryl acetate (II b) was prepared from ergosteryl acetate (I B) by a modification of Windaus' method (1) which raised the yield to about fifty per cent. The reactive system in ring B was

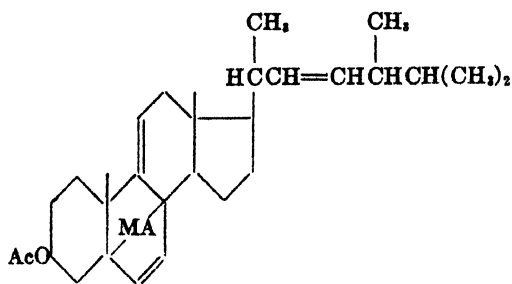
then protected by the addition of maleic anhydride (5). Of the three double bonds of the adduct (XV), the one at 6,7 is as unreactive as the corresponding bond of the ergosterol adduct (III), and the one at 22,23 is more reactive than that at 9,11. In order to facilitate preferential addition of oxygen to the 9,11-



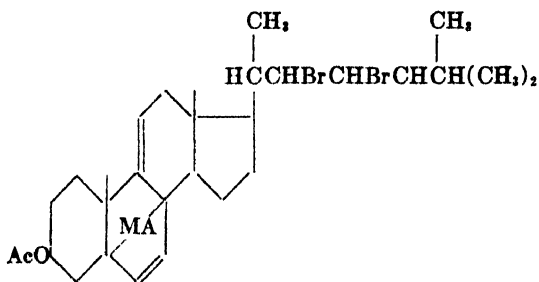
double bond, and to retain the 22,23-double bond for degradation of the side chain, the adduct was first converted to the known 22,23-dibromide (XVI) (5). Treatment of this bromide with perbenzoic acid readily afforded the 9,11-epoxide (XVII), m.p. 216–217°, which upon debromination with zinc in glacial acetic acid gave the desired maleic anhydride adduct of 9,11-oxidoergosteryl acetate, m.p. 220–221° (XVIII). Ozonolysis of this compound followed by oxi-

duction of the resulting aldehyde furnished the bisnor acid, which was isolated in the form of its methyl ester, m.p. 270–271° (XIX).

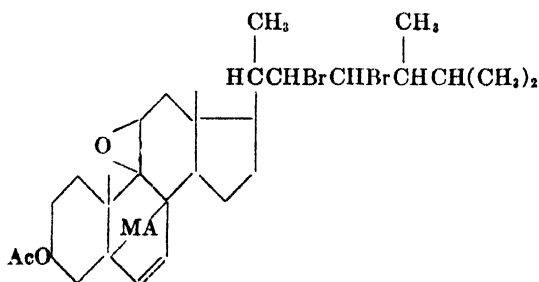
It was to be expected on the basis of the experience described above, that the pyrolytic elimination of maleic anhydride from (XIX) would give unsatisfactory results. In order to preserve the valuable supply of ester, the pyrolysis of the



XV



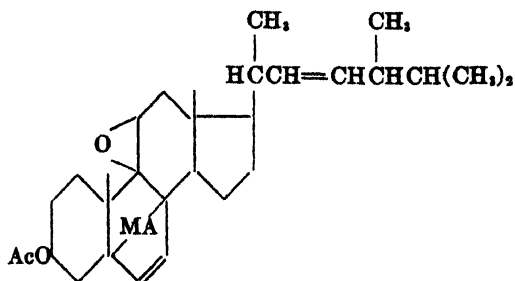
XVI



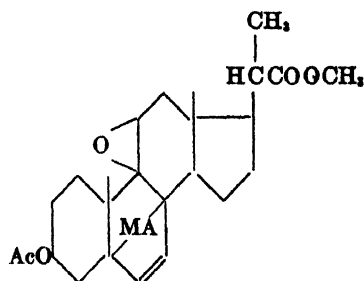
XVII

adduct of 9,11-oxidoergosteryl acetate (XVIII) was therefore first investigated. It afforded a volatile anhydride and an oil which after prolonged treatment with methanol eventually gave a crystalline product, m.p. 137–139°. The analytical values of this product indicated that the pyrolysis had been accompanied by a dehydrogenation to the extent of two atoms. The ease with which the product reacted with 2,4-dinitrophenylhydrazine suggested not only that the 9,11-epoxide has rearranged to an 11-ketone, but also that this ketone group is not sufficiently hindered to be unresponsive to the action of carbonyl reagents. The

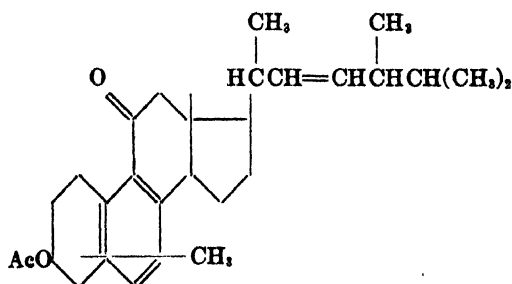
liberation of reactivity at C-11 makes it apparent that a radical structural change has taken place during the pyrolysis, such as is brought about for example by an aromatization of ring B. This view is supported by the absorption spectrum of the product, which with its maxima at $m\mu$ 257 (Log. E, 3.96) and $m\mu$ 305 (Log



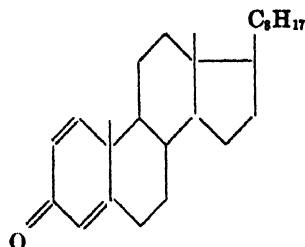
XVIII



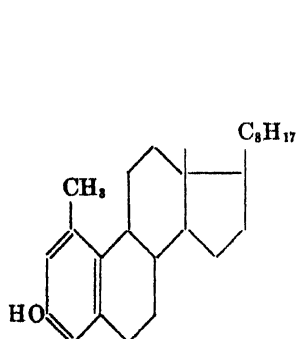
XIX



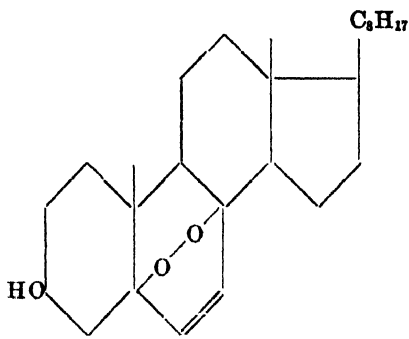
XX



XXI



XXII



XXIII

E, 3.37) shows resemblance to that of α -tetralone. The best known case in the steroid series of aromatization of ring B is the formation of neergosterol from bisergostatrienol (6, 7). Here aromatization is brought about by the loss of the angular methyl group in form of methane. The present reaction, however, must take a different course, because the loss of a carbon atom is contra-indicated not only by the analytical values for the reaction product, but also by the fact that no evolution of methane took place during the pyrolysis. It appears at present

most likely that aromatization was brought about by dehydrogenation, accompanied by a migration of the angular methyl group to a position as yet unknown (XX). The occurrence in the steroid series of such migration of angular methyl groups has first been demonstrated by Inhoffen (8, 9) by the rearrangement of the ketone (XXI) to the phenol (XXII).

The results of the exploratory studies outlined above demonstrate the feasibility of a side chain degradation of ergosterol and the introduction of oxygen at C-11 of this sterol. They are as yet, however, of little practical value. The principal disadvantage of the present method rests on the fact that the elimination of maleic anhydride from the oxidation and degradation products entails most serious losses. In the case of esters, the yield of desired material rarely exceeds thirty per cent, and in the case of carbonyl compounds it becomes almost inconsequential. Attempts to bring about fission of the adducts by less vigorous methods, such as heating them with large excesses of butadiene or cyclopentadiene have so far been unsuccessful. Substitution of the maleic anhydride adducts by the transannular peroxides of ergosterol (XXIII) (10) and dehydroergosterol (1) in the oxidation and degradation experiments has also been investigated. Because of the relatively high reactivity of the 6,7-double bond of these peroxides towards oxidizing agents and ozone, these studies have so far met with little success.

EXPERIMENTAL³

All melting points are corrected. All rotations were taken in chloroform at concentrations of about one per cent.

Maleic anhydride adduct of 22,23-oxidoergosteryl acetate (IV) A solution of ergosteryl acetate maleic anhydride adduct (III) in chloroform was treated with four equivalents of perbenzoic acid dissolved in chloroform. After forty-eight hours the solution was extracted with an aqueous sodium bicarbonate solution, washed with water, dried over sodium sulfate and evaporated to dryness. After several recrystallizations from ethyl acetate and methanol the oxide gave diamond-like crystals of m.p. 229–231°.

Anal. Calc'd for $C_{32}H_{48}O_6$: C, 73.9; H, 8.75.

Found: C, 73.8; H, 9.0.

Maleic anhydride adduct of 3(β)-acetoxybisor-5,7-choladien-22-al. (V). A stream of 9% ozone was passed through a vigorously stirred suspension of 5.36 g. of finely ground ergosteryl acetate-maleic anhydride adduct, (III) in 120 cc. of glacial acetic acid until a clear solution had been obtained. During the reaction the temperature was kept at 20°. After five additional minutes the ozonization was discontinued, and the temperature of the solution was reduced to 15°. With stirring, 8 g. of zinc dust was then gradually added, and after 15 minutes 1 cc. of a 1% solution of silver nitrate. The stirring was continued until the solution gave a negative test with starch-iodide paper, which generally required about one hour. The unreacted zinc dust was then filtered by suction and washed with 100 cc. of glacial acetic acid. The combined filtrate and washing were poured into one liter of water, and the amorphous, white precipitate which immediately formed was filtered, washed with water and dried *in vacuo* at 2 mm. over potassium hydroxide. Addition of petroleum ether to a solution of the aldehyde in ethyl acetate afforded a nicely crystalline precipitate, which after two recrystallizations from the same combination of solvents melted at 206–208°, $[\alpha]_D^{25} -15.4^\circ$; yield 75%.

³ In cooperation with J. A. Klacsmann.

Anal. Calc'd for $C_{28}H_{36}O_6$: C, 71.8; H, 7.75.

Found: C, 71.8; H, 8.0.

2,4-Dinitrophenylhydrazone of (V). An excess of a 1% solution of 2,4-dinitrophenylhydrazine in ethanol containing 1% of hydrochloric acid was added to a 1% solution of the aldehyde (V) in ethyl acetate. The hydrazone, which formed instantaneously, was recrystallized several times from ethyl acetate; m.p. 246°.

Anal. Calc'd for $C_{34}H_{40}N_4O_8$: C, 63.0; H, 6.2.

Found: C, 63.0; H, 6.3.

Maleic anhydride adduct of methyl 3(β)-acetoxybisor-5,7-choleadienate (VI b). To a solution of 4.4 g. of the crude, amorphous aldehyde (V) in 50 cc. of glacial acetic acid was added dropwise over a period of forty-five minutes a solution of 2 g. of chromic acid anhydride in the minimum amount of water and 5 cc. of glacial acetic acid. During the reaction the temperature was kept below 20°. After four hours the excess reagent was reduced by sodium bisulfite, and the mixture poured into 1 N sulfuric acid. The amorphous precipitate was filtered, washed with water, and dried *in vacuo*; yield 85–88%. The crude acid (VI a), 4.1 g., was dissolved in 200 ml. of ether and some insoluble, greenish material removed by centrifugation. To the clear solution was then added diazomethane, dissolved in ether, until a yellow color persisted for at least ten minutes after the last addition. During the reaction the sparingly soluble ester began to crystallize. It was recrystallized several times from glacial acetic acid; m.p. 272°; $[\alpha]_D^{25} -10.8^\circ$; yield 85%.

Anal. Calc'd for $C_{29}H_{38}O_7$: C, 69.8; H, 7.7; CH_3O , 6.2; CH_3CO , 8.6.

Found: C, 69.2; H, 7.5; CH_3O , 6.7; CH_3CO , 8.1.

Maleic anhydride adduct of 3(β)-hydroxybisor-5,7-choleadienic acid (VII a). An ether solution of the crude monocarboxylic acid described above was thoroughly shaken with 4 N sodium hydroxide. This treatment brings about an opening of the anhydride ring and hydrolysis of the 3-acetoxy group. Acidification of the alkaline layer afforded the tricarboxylic acid (VII a), which after several recrystallizations from dilute acetic acid melted with decomposition at 277–281°. Upon drying *in vacuo* at 100° the acid forms the anhydride.

Anal. Calc'd for $C_{28}H_{34}O_8$: C, 70.6; H, 7.7.

Found: C, 70.4; H, 7.7.

Trimethyl ester of the maleic acid adduct of 3(β)-acetoxybisor-5,7-choleadienic acid (VII b). An excess of diazomethane dissolved in ether was added to a methanol solution of the tricarboxylic acid (VII a) described above. After several hours the solvent and excess diazomethane were removed *in vacuo* and the residual oil was refluxed with acetic anhydride for forty minutes. Upon cooling, the ester separated in nice, hexagonal prisms. After two recrystallizations from acetic anhydride it melted at 184–185°; $[\alpha]_D^{25} -30.0^\circ$; yield 50%.

Anal. Calc'd for $C_{31}H_{44}O_8$: C, 68.4; H, 8.1; CH_3O , 17.1.

Found: C, 67.6; H, 8.3; CH_3O , 16.2.

Maleic anhydride adduct of 3(β)-acetoxybisor-5,7-choleadienic acid (VI a). The crude tricarboxylic acid (VII a) described above was refluxed for twenty minutes with acetic anhydride, and the crystalline material which separated upon cooling was recrystallized from the same solvent; m.p. 260°.

Anal. Calc'd for $C_{28}H_{36}O_7$: C, 69.4; H, 7.5.

Found: C, 69.2; H, 7.7.

Methyl 3(β)-acetoxybisor-5,7-choleadienate (VIII b). One-gram samples of the adduct (VI b) were heated in a small retort at 20–30 mm. and 280° for twenty-five minutes. The maleic anhydride which had distilled over was then removed, and the heating of the retort continued at 230–250° and 0.001 mm. There was obtained an oily distillate which upon digestion with methanol became crystalline. Numerous recrystallizations from methanol eventually gave the ester in the form of nice plates, m.p. 147°; $[\alpha]_D^{25} -83^\circ$; yield 30%.

Anal. Calc'd for $C_{28}H_{36}O_4$: C, 74.8; H, 9.6; CH_3O , 7.7.

Found: C, 74.7; H, 8.9; CH_3O , 7.8.

Methyl 3(β)-hydroxybisor-5,7-choleadienate (VIII a). To a warm methanol solution of

the methyl ester (VIII b) was added 6 cc. of a 1% solution of potassium hydroxide in methanol. The mixture was kept in the dark for twelve hours, and the long, spike-like crystals, which had separated were filtered, and recrystallized from methanol; m.p. 163-165°; $[\alpha]_D^{25}$ -120°; yield 72%.

Anal. Calc'd for $C_{23}H_{34}O_4 \cdot H_2O$: C, 73.4; H, 9.5.

Found: C, 73.4; H, 9.1.

Methyl 3(β)-acetoxybisnor-7-cholenate (IX). A 5% solution of the acetoxy ester (VIII b) in neutral ethyl acetate was shaken with hydrogen and a platinum black catalyst at room temperature. Hydrogen uptake ceased after slightly more than one equivalent of hydrogen had been consumed. The filtered solution was evaporated to dryness, and the residue recrystallized several times from methanol; m.p. 136°; $[\alpha]_D^{25}$ -4.2°; yield 70%.

Anal. Calc'd for $C_{23}H_{34}O_4$: C, 75.0; H, 9.1.

Found C, 74.8; H, 9.2.

Maleic anhydride adduct of 3(β)-acetoxy-20-bromobisnor-5,7-choladien-22-al (X). A 1% solution of bromine in glacial acetic acid was gradually added to a solution of 0.52 g. of the aldehyde (V) in 6 cc. of glacial acetic acid. In the presence of sunlight, decolorization took place rapidly under formation of hydrogen bromide until about one equivalent of bromine had been consumed. The solution was then evaporated to dryness *in vacuo*, and the residual oil dissolved in ethyl acetate. Upon addition of petroleum ether a nicely crystalline precipitate was formed, which after recrystallization from ethyl acetate-petroleum ether melted at 180°.

Anal. Calc'd for $C_{23}H_{34}BrO_4$: C, 61.4; H, 6.4; Br, 14.6.

Found: C, 61.9; H, 6.6; Br, 14.9.

Enol acetate of 3(β)-acetoxybisnor-5,7-choladien-22-al (XI) or (XII). A mixture of 0.51 g. of the aldehyde (V), 0.2 g. of freshly fused sodium acetate and 10 cc. of acetic anhydride was heated in a nitrogen-filled, sealed tube for five hours at 175°. The content of the tube was then washed with acetic anhydride into a distilling flask and evaporated to dryness *in vacuo*. The residue was then thoroughly extracted with ether, the extract evaporated, and the product dissolved in ethyl acetate. Upon addition of petroleum ether, the enol acetate crystallized in needle-like prisms. It was recrystallized from a mixture of ethyl acetate and petroleum ether; m.p. 189-190°; yield 60%.

Anal. Calc'd for $C_{26}H_{38}O_7$: C, 70.6; H, 7.5.

Found: C, 70.6; H, 7.5.

Ozonization of the enol acetate. A stream of ozone was passed through a vigorously stirred suspension of 0.26 g. of finely ground enol acetate in 3.5 cc. of glacial acetic acid at 20°. The ozonization was discontinued five minutes after all material had become dissolved, and zinc dust and a drop of silver nitrate were added. The stirring was continued until the mixture no longer gave a positive test with starch-iodide paper. The filtered solution was then poured into water and the precipitate collected, washed, and dried (0.23 g.). It was dissolved in 7 cc. of acetic acid, and the solution treated with 0.1 g. of chromic acid anhydride. After three hours the excess reagent was reduced with methanol, and the reaction product precipitated with water. It was dissolved in ether, and the solution washed with dilute sodium carbonate. Evaporation of the ether gave a neutral residue which after recrystallization from acetic acid gave clusters of rectangular plates, m.p. 287°.

Anal. Calc'd for $C_{25}H_{36}O_6$: C, 70.4; H, 7.0.

Found: C, 70.3; H, 7.0.

Dehydroergosteryl acetate (II b). A solution of 325 g. of mercuric acetate in 5.2 liters of glacial acetic acid was added to 200 g. of ergosteryl acetate dissolved in 2.8 liters of chloroform, and the mixture shaken for eighteen hours. The mercurous acetate was then removed and washed with ether, and the combined filtrate and washings were concentrated *in vacuo* at a temperature not exceeding 45°. The crystalline precipitate which formed was collected and washed with acetic acid and methanol. Concentration of the mother liquor gave a second fraction. The fractions were combined, dissolved in ether, and the solution was filtered and concentrated until crystals began to separate. One liter of ethanol was then

added and the mixture heated until most of the ether had evaporated. The crystalline material which separated upon cooling weighed 86.3 g., m.p. 143–146°; yield 43%. Concentration of the mother liquor gave an additional crop of 9 g. of somewhat less pure material.

Dehydroergosteryl acetate-maleic anhydride adduct (XV). A solution of 86.3 g. of dehydroergosteryl acetate and 65.5 g. of maleic anhydride in 225 cc. of benzene was refluxed for four hours. The benzene and excess maleic anhydride were then removed *in vacuo* at a temperature not exceeding 100°. The residue was digested with a small amount of ether and dried; yield 82.2 g. or 78%. After recrystallization from acetic acid the adduct melted at 228–229°. The m.p. reported by Honigsmann (5) is 220–240°.

22,23-Dibromodehydroergosteryl acetate-maleic anhydride adduct (XVI) (5). A cooled solution of 11.5 g. of bromine in 25 cc. of chloroform was slowly added to an ice-cold solution of 38.4 g. of dehydroergosteryl acetate-maleic anhydride adduct in 120 cc. of chloroform. The solvent was then removed *in vacuo* and the residue recrystallized from a mixture of acetone and methanol; m.p. 235–236°, $[\alpha]_D^{25} +68.8^\circ$; yield 36.4 g. or 73%.

Anal. Calc'd for $C_{28}H_{46}Br_2O_6$: Br, 23.0. Found: Br, 23.0.

22,23-Dibromo-9,11-oxido-dehydroergosteryl acetate-maleic anhydride adduct (XVII). A solution of 9.54 g. of the dibromide (XVI) in 100 cc. of chloroform was treated with 73 cc. of a 0.252 *N* solution of perbenzoic acid in chloroform. The solution was kept at 4° for six days, and was then washed with 2% sodium hydroxide and water, dried over potassium carbonate and evaporated to dryness. The residue was dissolved in acetone and the solution freed from some insoluble material by centrifugation. It was concentrated *in vacuo* until crystallization began, which was brought to completion by addition of methanol. The oxide was then recrystallized from a mixture of acetone and methanol; m.p. 216–217°, yield 7.6 g. or 80%.

Anal. Calc'd for $C_{28}H_{46}Br_2O_6$: Br, 22.5. Found: Br, 22.5.

9,11-Oxido-dehydroergosteryl acetate-maleic anhydride adduct (XVIII). A total of 112 g. of zinc dust was added in small portions to a vigorously stirred solution of 5.6 g. of the dibromo oxide (XVII) in 400 cc. of warm glacial acetic acid. The reaction temperature was kept at 105–110°. After five hours, the hot solution was filtered and the zinc dust was washed thoroughly with warm acetic acid. The combined filtrate and washings were poured into water, and the precipitate was filtered and recrystallized several times from acetic acid; m.p. 220–221°; yield 2.9 g. or 70%.

Anal. Calc'd for $C_{28}H_{46}O_6$: C, 74.2; H, 8.4.

Found: C, 74.5; H, 8.7

Maleic anhydride adduct of methyl 3(β)-acetoxy-9,11-oxido-Δ^{5,7}-choleadienate (XIX). A rapid stream of ozone (9%) was passed through a vigorously stirred suspension 1.1 g. of the 9,11-oxide (XVIII) in 25 cc. of acetic acid. After about twenty minutes, when all material had gone into solution, ozonization was discontinued and zinc dust and a drop of silver nitrate solution were added with stirring. When the solution no longer gave a positive test with starch-iodide paper it was filtered, and the filtrate poured into water. The amorphous material was collected, washed with water and dried. It readily reacted with 2,4-dinitrophenylhydrazine. The product was dissolved in 20 cc. of glacial acetic acid and the solution treated with 0.04 g. of chromic acid anhydride over a period of three hours. The excess reagent was then reduced by the addition of sodium bisulfite, and the solution poured into water. The precipitate was collected, washed with water, dried, and dissolved in ether. The filtered solution was then treated with an excess of diazomethane. The ester crystallized at once in form of glittering prisms. It was recrystallized from acetic acid; m.p. 270–271°; yield 42%.

Anal. Calc'd for $C_{29}H_{48}O_8$: C, 67.7; H, 7.4; CH_3O , 6.0.

Found: C, 67.6; H, 7.2; CH_3O , 6.4.

Pyrolysis of the maleic anhydride adduct of 9,11-oxido-ergosteryl acetate (XVIII). Small portions of the adduct were heated in a retort at 10 mm. pressure to 275–285° for from fifteen to twenty minutes until the anhydride had ceased to come over. The retort was then cooled

to 200° and the pressure reduced to 0.001 mm. An oily distillate was obtained, which after prolonged digestion with small amounts of methanol began to crystallize. After repeated recrystallizations from methanol the substance was obtained in form of well defined prisms; m.p. 137-139°; yield 15-30%.

Anal. Calc'd for $C_{30}H_{42}O_2$: C, 80.0; H, 9.4.

$C_{30}H_{44}O_2$: C, 79.6; H, 9.8.

Found: C, 79.9; H, 9.3.

The compound readily reacts with 2,4-dinitrophenylhydrazine. Absorption spectrum: maxima at 257 m μ (Log. E, 3.96) and 305 m μ (Log. E, 3.37).

SUMMARY

The degradation of ergosterol to derivatives of 3(β)-hydroxybisor-5,7-choladienic acid, 3(β)-hydroxybisor-5,7-choladiene-22-al and 3(β)-hydroxy-9,11-oxibisor-5,7-choladienic acid has been described.

NEW HAVEN, CONN.

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ERGOSTEROL F¹

WERNER BERGMANN AND JOHN A. KLACSMANN

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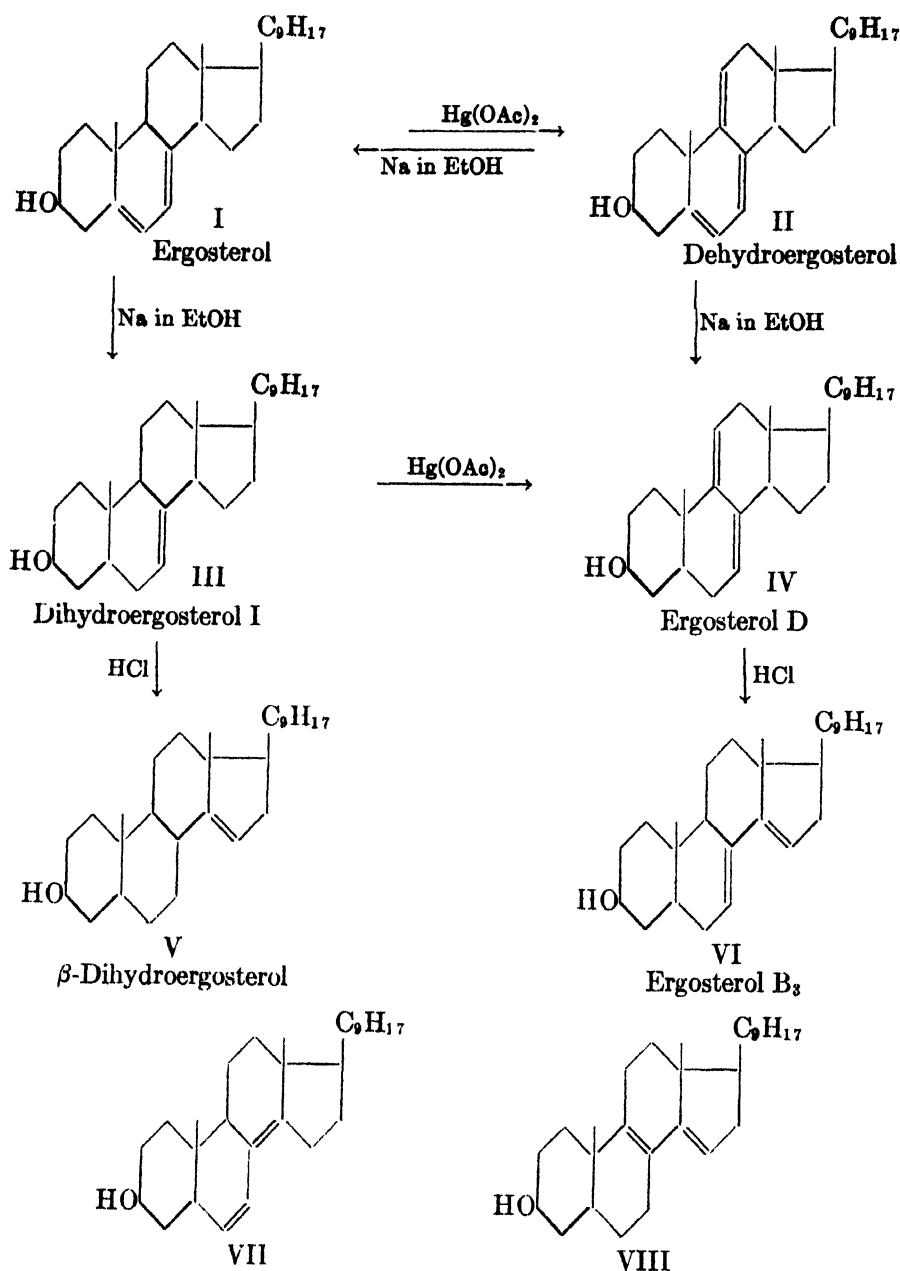
In connection with the studies on the conversion of ergosterol (I) to adrenal cortical hormones, which have been discussed in the preceding paper (1), a search was made for derivatives of ergosterol which possess unsaturation at C-11 and which do not require protection by maleic anhydride during the alteration of the molecule. One of the more promising isomers of ergosterol appeared to be ergosterol F which had been prepared by Windaus and collaborators (2) by the reduction of dehydroergosterol (II) with sodium in ethanol. After it had become evident that certain "isomers" of ergosterol lack uniformity (3), Nakamiya, working in Windaus' laboratory, reinvestigated ergosterol F (4). He found that heating this sterol with maleic anhydride gave about forty per cent of a complex reaction product. The unreacted material possessed physical properties identical with those of the starting material, a fact which Nakamiya interpreted as proof for the uniformity of ergosterol F.

Without giving specific reasons, it has been suggested by Sobotka (5) that ergosterol F possesses structure VII. The present authors, however, regarded it as more likely that the cyclic double bonds of this sterol were at 7,8 and 9,11 (IV), and that the sterol was formed from dehydroergosterol (II) by the addition of hydrogen to the 5,6-double bond. Such preferential reductions, seemingly unaccompanied by migration of the unreacted double bonds are well known in this series. Thus ergosterol (I) upon reduction with sodium in ethanol affords dihydroergosterol I (III) and with a catalyst γ -ergosterol (6).

The physical properties of ergosterol F and its derivatives prepared in this laboratory by Windaus' method (2) agreed with those reported in the literature. In the course of a preliminary study of the chemistry of ergosterol F, doubts arose once more concerning its homogeneity. They were strengthened by a critical analysis of certain statements made in the literature in regard to this compound. Thus the reported maxima of the absorption spectrum of ergosterol F (2) while at the expected wave length are of such low intensity as to indicate that the absorption is due to the presence of an impurity. It was also found difficult to understand that dehydrogenation of ergosterol followed by hydrogenation should give ergosterol F, while hydrogenation followed by dehydrogenation affords a different isomer, ergosterol D (7). Since the experimental conditions in both sequences of reactions are quite similar, the formation of identical final products might be expected.

¹ The work described in this paper was done under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Yale University.

In the course of testing the homogeneity of ergosterol F recourse was taken to reactions which are known to be typical of certain systems of unsaturation.



Thus steroids, which like ergosterol (I) possess a system of conjugated double bonds in ring B, are readily dehydrogenated by eosin in the presence of light to give difficultly soluble, high melting "bi-steroids" (9, 10, 11, 12). When sub-

jected to such dehydrogenation, ergosterol F gave about ten per cent of a bi-compound which like the corresponding derivative of ergosterol melted at 202–203° (9) and gave neoergosterol m.p. 151°; $[\alpha]_D^{22} -12.5^\circ$, upon heating (13). This evidence therefore established the presence in ergosterol F of about ten per cent of ergosterol. It is supported by the absorption spectrum of ergosterol F (Figure 1) which shows the presence of about six per cent of ergosterol.

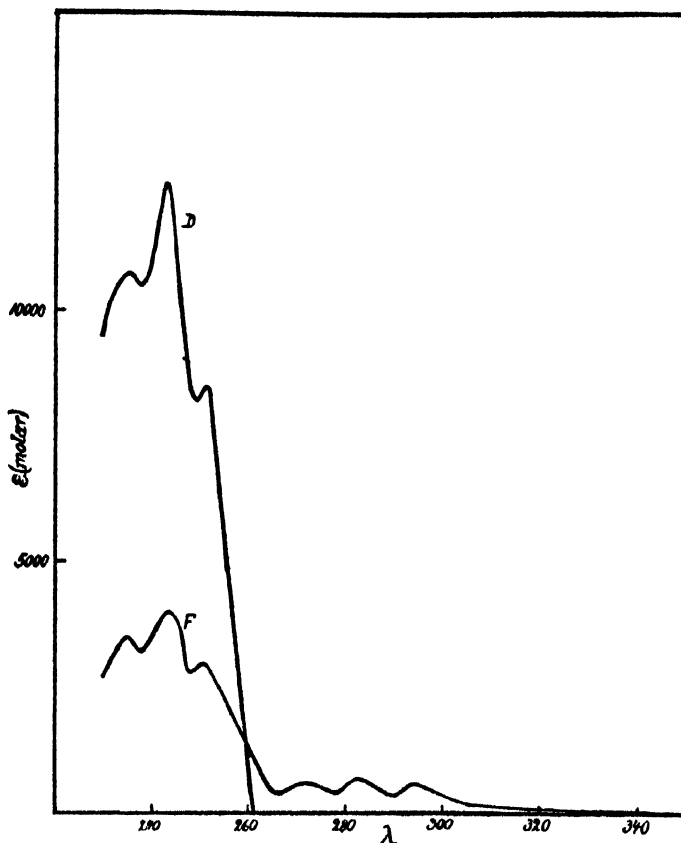


FIG. 1. ABSORPTION SPECTRA OF ERGOSTEROL-F (F) AND ERGOSTERYL-D-ACETATE (D)

Frequent recrystallizations of the acetate of the soluble, unreacted fraction from the photodehydrogenation of ergosterol F eventually gave a product, the physical properties of which, m.p. 169°; $[\alpha]_D +22^\circ$, showed closest similarity to those of ergosteryl-D acetate.

A comparison of the absorption spectrum (Figure 1) of the present acetate with that of ergosterol D (7, 8) demonstrated the identity of the two compounds. Since the absorption spectra of ergosterols F and D are closely similar with the exception of the maxima which are unusually low in the former, it may now be concluded that the absorption of ergosterol F (Figure 1) is due to the presence of ergosterol D, which represents about thirty-five per cent of the mixture.

Taking into consideration that ergosterol F contains beside ergosterol D also

about ten per cent ergosterol, it follows that the remainder of the mixture is represented by one or more compounds devoid of absorption in the ultraviolet region. Successful isolation of such a product was eventually achieved by repeated recrystallizations of ergosteryl-F benzoate, saponification of the final fraction and further recrystallizations of the sterol. The compound thus obtained no longer showed absorption in the ultraviolet and proved to be identical with 5,6-dihydroergosterol (dihydroergosterol I), m.p. 170°; $[\alpha]_D -18^\circ$.

The assumption that ergosterol F is unsaturated at 7,8 and 9,11 had been the starting point of the present investigation. After it had been demonstrated that this sterol is not an isomer of ergosterol but a mixture consisting principally of dihydroergosterol and ergosterol D, it appeared reasonable to assign to ergosterol D the structure (IV) which originally had been assumed to be that of ergosterol F. This formulation explains the observed experimental facts better than the one (VIII) originally proposed by Callow (14). A similar conclusion based substantially on molecular rotation differences has recently been arrived at by Barton (15). For analogous reasons that same author has also questioned the uniformity of ergosterol F.

It now appears that the reduction of dehydroergosterol (II) proceeds along two different routes. In the one the over-all effect is the addition of one mole of hydrogen to the 5,6-double bond to give ergosterol D (IV). Since this is a sterol with conjugated double bonds extending over two rings it is inert to the action of sodium in alcohol (16, 17), and therefore remains unchanged under the conditions of the reaction. In the second route the first steps involve the disappearance of the 9,11-double bond of dehydroergosterol (II) with the formation of ergosterol (I), small amounts of which may be detected in the reaction mixture. The bulk of the ergosterol, however, undergoes further hydrogenation in the well known manner to give 5,6-dihydroergosterol, for which formula (III) has been definitely established (6, 15). It is of interest to note in this connection, that according to Windaus and collaborators (3) heating dehydroergosterol with sodium ethoxide at 185° affords a fraction precipitable with digitonin, which contains ergosterol D and a compound similar to dihydroergosterol. Windaus and collaborators (2) have also reported that the hydrogenation of dehydroergosterol (II) with sodium in isopropanol affords dihydroergosterol II. The fact that this rather ill-defined sterol shows absorption in the ultraviolet at once demonstrated the presence of some material with conjugated cyclic bonds. On the basis of experiences gained with ergosterol F, it is now safe to conclude that dihydroergosterol II is also a mixture consisting principally of ergosterol D and 5,6-dihydroergosterol. The reported absorption spectrum for dihydroergosterol II (2) shows maxima at the same wave lengths as those of ergosterol D, and of an intensity corresponding to the presence in the mixture of about forty per cent of this sterol.

According to Nakamiya, treatment of ergosterol F with hydrochloric acid leads to the well characterized ergosterol B₃ (VI) and the new ergosterol G. It now appears certain that the progenitor of the former has been the ergosterol D present in the mixture. Ergosterol G, which is devoid of ultraviolet absorp-

tion, might conceivably be regarded as the rearrangement product of the 5,6-dihydroergosterol present in ergosterol F. Its reported physical properties, however, contra-indicate its identity with the expected β -dihydroergosterol (V) (8). It seems at present most likely that ergosterol G is a mixture, as has already been suggested by Barton (15).

CONCLUSIONS

It has been demonstrated that ergosterol F is a mixture consisting of approximately equal parts of ergosterol D and dihydroergosterol and small amounts of ergosterol.

It has been suggested that dihydroergosterol II is a mixture of similar composition and that ergosterol G lacks homogeneity.

NEW HAVEN, CONN.

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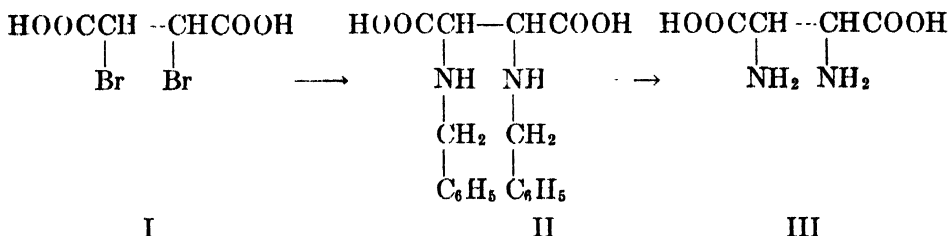
MESO- α,β -DIAMINOSUCCINIC ACID

WILHELM WENNER

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For the purpose of synthesizing biotin, meso- α,β -diaminosuccinic acid appears to be a convenient starting material. Since the methods described for its preparation (4, 11, 13, 15, 16, 18) have drawbacks, which become especially serious if considerable amounts of the acid are needed, a new synthesis was devised.

It consists in the following sequence of reactions: meso- α,β -Dibromosuccinic acid (I) is reacted with benzylamine to meso- α,β -bis(benzylamino)succinic acid II, which was first isolated by Frankland (5, 6). The preparation of this acid was considerably improved, affording yields of 80% and higher. As an intermediate in the reaction between meso- α,β -dibromosuccinic acid and benzylamine the dibenzylamine salt of meso- α,β -bis(benzylamino)succinic acid was isolated.



meso- α,β -Bis(benzylamino)succinic acid is debenzylated by catalytic hydrogenation in the presence of at least one equivalent of hydrochloric or hydrobromic acid. This is an extension of the well known method of catalytic debenzylation (1, 2, 3, 7) to a compound containing two benzylamino groups in the same molecule. The free acid or its alkali salts cannot be debenzylated. Palladium on charcoal as catalyst is superior to platinum oxide.

The yield of meso- α,β -diaminosuccinic acid (III) is about 90% of the theoretical. The method is suitable for large scale manufacture, making meso- α,β -diaminosuccinic acid an easily accessible compound (17).

When instead of the meso- the *dl*- α,β -dibromosuccinic acid (8, 12) is reacted with benzylamine, an α,β -bis(benzylamino)succinic acid m.p. 210–212° is obtained in considerably lower yield, obviously because *dl*- α,β -dibromosuccinic acid is by far less stable than the meso acid (6, page 2880) and is split to a large extent into bromomaleic acid.

Hydrogenation of this *dl*-bis(benzylamino)succinic acid does not yield the expected *dl*- α,β -diaminosuccinic acid, but the meso acid. The *dl*- α,β -diaminosuccinic is probably formed originally but isomerizes into the meso acid under the influence of the mineral acid. Such a conversion has been observed previously by Kuhn and Zumstein (10). Obviously this rearrangement is facilitated during the cleavage of the benzyl groups. The identity of the meso- α,β -diaminosuccinic acid was established by conversion into the dibenzoyl derivative which

melted at 208–210° in agreement with the results of Kuhn and Zumstein (9) who reported m.p. 212–213° for the dibenzoyl derivative of the meso acid. The dibenzoyl derivative of the racemic acid melts at 164°.

The debenzylation procedure allows the correlation between the structure of the α,β -bis(benzylamino)succinic acids and the α,β -diaminosuccinic acids which was hitherto impossible. The direct interconversion of meso- α,β -bis(benzylamino)succinic acid into meso- α,β -diaminosuccinic acid confirms Frankland's assumption that substitution of the bromo atoms by benzylamino groups in meso- α,β -dibromosuccinic acid occurs without change in the steric arrangement.

EXPERIMENTAL

The melting points are uncorrected.

1. *meso- α,β -Bis(benzylamino)succinic acid*. A. *Without solvent*. Fifty grams of meso- α,β -dibromosuccinic acid (14) is added in portions to 150 g. of benzylamine with stirring at 80°. After complete addition, the mixture is heated for two hours to 90–100°, then cooled to room temperature and 500 cc. of water added. The solution is treated with charcoal and filtered. The filtrate is made Congo acid by addition of dilute hydrochloric acid. meso- α,β -Bis(benzylamino)succinic acid separates as a colorless microcrystalline powder. It is filtered and washed with water; yield 50–55 g. (84–92%). The crude acid is dissolved in dilute sodium hydroxide solution, treated with charcoal, filtered, and the filtrate acidified with acetic acid. Thus prepared, meso- α,β -bis(benzylamino)succinic acid melts at 218–219°. If the acid is repeatedly precipitated from alkaline solution the melting point rises to 230°.

Anal. Calc'd for $C_{18}H_{26}N_2O_4$: C, 65.84; H, 6.14; N, 8.53.

Found: C, 65.90; H, 6.27; N, 8.71.

B. *In alcohol*. To a stirred solution of 250 g. of meso- α,β -dibromosuccinic acid in 2 liters of alcohol, 855 g. of benzylamine are added slowly. After complete addition the mixture is heated on the steam-bath for 5–6 hours. A heavy precipitate of the dibenzylamine salt of meso- α,β -bis(benzylamino)succinic acid appears (see C). After cooling to about 40–50° about 1 liter of water is added, then conc'd hydrochloric acid in small portions until pH 1–2 is reached (about 250–270 cc.). The pH is then adjusted with conc'd sodium acetate solution to pH 4–5. The mixture is filtered by suction. The crystals are washed with water and alcohol until colorless. meso- α,β -bis(benzylamino)succinic acid is obtained in a yield varying from 320 to 380 g. (80–91%). The acid melts generally at 213–217°. Recrystallization from acetic acid with addition of water raises the m.p. to 225°.

Anal. Calc'd for $C_{18}H_{26}N_2O_4$: C, 65.84; H, 6.14; N, 8.53.

Found: C, 66.13, 65.62; H, 6.29, 5.94; N, 8.65, 8.54.

Instead of alcohol, methanol can be used as solvent.

From the original mother liquor the excess benzylamine is recovered by addition of potassium hydroxide and distillation.

C. *Dibenzylamine salt of meso- α,β -bis(benzylamino)succinic acid*. If the reaction mixture from B above after heating is diluted with about three volumes of water, the dibenzylamine salt crystallizes. It is filtered and washed with cold water. Recrystallization from water yields colorless prisms of m.p. 211–222°.

Anal. Calc'd for $C_{22}H_{30}N_4O_4$: C, 70.82; H, 7.06; N, 10.33.

Found: C, 70.11; H, 6.73; N, 10.40.

D. *Monohydrochloride*. One gram of meso- α,β -bis(benzylamino)succinic acid is dissolved in 6 cc. of conc'd hydrochloric acid and 10 cc. of water at 90–100°. Upon cooling, the hydrochloride crystallizes. It is filtered and dried without washing in order to prevent hydrolysis.

Anal. Calc'd for $C_{18}H_{26}N_2O_4 \cdot HCl$: Cl, 9.95. Found: Cl, 10.37.

E. *Dihydrobromide*. Ten grams meso- α,β -bis(benzylamino)succinic acid is dissolved

in 20 cc. of 48% hydrobromic acid by warming on the steam-bath. The solution is cooled in a refrigerator for several hours. The dihydrobromide is filtered, washed with some conc'd hydrobromic acid, and dried in a desiccator; yield 18-19 g., m.p. 155° (dec.).

Anal. Calc'd for $C_{18}H_{20}N_2O_4 \cdot 2HBr$ (490.22): C, 44.10; H, 4.52; N, 5.71.

Found: C, 44.20; H, 4.81; N, 5.55.

F. Separation of mixtures of meso- α,β -bis(benzylamino)succinic acid and meso- α,β -diaminosuccinic acid. One-half gram of meso- α,β -bis(benzylamino)succinic acid and 0.5 g. of meso- α,β -diaminosuccinic acid are mixed and suspended in 50 cc. of absolute alcohol. Two cc. of aqueous hydrochloric acid (35%) is added. The mixture is shaken for one hour at room temperature, and is then filtered. The undissolved material is pure meso- α,β -diaminosuccinic acid of m.p. 303°; yield 0.48 g.

Anal. Calc'd for $C_8H_{10}N_2O_4$: C, 32.43; H, 5.44; N, 18.91.

Found: C, 31.84; H, 5.74; N, 18.63.

The filtrate is concentrated to a small volume. Upon addition of water, crystallization starts immediately. Filtration gives 0.4 g. of meso- α,β -bis(benzylamino)succinic acid of m.p. 230°.

2. meso- α,β -Diaminosuccinic acid. **A. In water.** Three grams of meso- α,β -bis(benzylamino)succinic acid is dissolved in 50 cc. of hydrochloric acid (10%). The solution is hydrogenated with one gram of palladium charcoal (10% Pd) at 25° and 500 lbs. pressure for 20 hours. It is filtered and distilled to dryness *in vacuo*. The crystalline residue is dissolved in dilute sodium hydroxide and filtered. The clear filtrate is acidified with acetic acid. meso- α,β -Diaminosuccinic acid separates immediately. It is filtered, washed with water, and dried at 60°. The yield of material melting at 281-284° (dec.)¹ is 0.6 g.

Anal. Calc'd for $C_8H_{10}N_2O_4$: C, 32.43; H, 5.44.

Found: C, 32.47; H, 6.05.

B. In methanol Five grams of meso- α,β -bis(benzylamino)succinic acid and 70 cc. of methanol are placed into the glass liner of a shaking autoclave. Five cc. of conc'd hydrochloric acid and 2 g. of palladium charcoal (20% Pd) are added. The mixture is hydrogenated at room temperature and 1000 lbs. pressure for 16 hours. The solution is filtered from the catalyst and distilled to dryness. The residue is dissolved in dilute sodium hydroxide and filtered. Addition of acetic acid to the filtrate precipitates meso- α,β -diaminosuccinic acid at once. It is filtered, dissolved cold in the minimum quantity of 10% hydrochloric acid, filtered, and diluted to five times its volume with water. On standing, the pure acid crystallizes slowly. It is filtered after 24 hours and dried; m.p. 303-305° (dec.).

Anal. Calc'd for $C_8H_{10}N_2O_4$: C, 32.43; H, 5.44.

Found: C, 32.24; H, 5.84.

C. In acetic acid In a glass-lined autoclave 150 g. of meso- α,β -bis(benzylamino)succinic acid, 650 g. of acetic acid, 140 g. of hydrochloric acid (35%), and 25 g. of palladium charcoal (containing 2.5 g. of palladium) are hydrogenated at 800 lbs. The temperature is kept for 15 hours at 35°, for six hours at 50-60° and finally for 15 hours at 20°. The mixture is treated with 10% aqueous hydrochloric acid in order to dissolve the precipitated hydrochloride of meso- α,β -diaminosuccinic acid at 80°. The hot solution is filtered by suction from the catalyst. The latter is washed thoroughly with 10% hydrochloric acid. The combined filtrates are distilled to dryness in a vacuum. The residue is stirred with distilled water and cooled in a refrigerator for 20 hours. The colorless crystals are filtered, washed with water and dried; yield 59 g. (90%) of meso- α,β -diaminosuccinic acid of m.p. 305-306° (dec.).

3. dl- α,β -Bis(benzylamino)succinic acid. Thirty grams of dl- α,β -dibromosuccinic acid (8, 12) is stirred with 200 cc. of ethanol at room temperature. Ninety cc. of benzylamine is added slowly. The mixture is refluxed for five hours with stirring. The formed crystalline precipitate is filtered and washed with cold alcohol. It is stirred up with 100 cc. of

¹ Kuhn and Zumstein (9, page 1430) claim that diaminosuccinic acids do not have definite melting or decomposition points. We find distinct decomposition points which, however, vary considerably depending upon the rate of heating.

water. Twenty cc. of acetic acid is added. The crystals which separate are filtered and dissolved in 40 cc. of 3 *N* sodium hydroxide and 90 cc. of water. The cold solution is treated with charcoal, filtered, and the filtrate is acidified with acetic acid. *dl*- α,β -Bis(benzylamino)succinic acid separates colorless. It is filtered, washed with water, and dried; yield 13 g., m.p. 210–212°. Reprecipitation from alkaline solution raises the m.p. to 215°.

Anal. Calc'd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53.

Found: C, 66.29; H, 6.31; N, 8.34.

Hydrochloride. One gram of the acid is warmed with 5 cc. of 3 *N* hydrochloric acid. The acid does not dissolve, but forms a voluminous hydrochloride. To isolate the hydrochloride, 1 g. of the acid is dissolved in 10 cc. of conc'd hydrochloric acid and 15 cc. of water at 80°. The solution is filtered immediately and diluted with 20 cc. of water. On standing at room temperature for 24 hours, 0.7 g. of the monohydrochloride separates, melting at 175–176° (dec.).

Anal. Calc'd for $C_{18}H_{20}N_2O_4 \cdot HCl$: C, 59.26; H, 5.80; N, 7.68; Cl, 9.73.

Found: C, 59.22; H, 5.69; N, 7.89; Cl, 9.62.

Hydrobromide. Ten grams of *dl*-bis(benzylamino)succinic acid is stirred with 40 cc. of hydrobromic acid (48%). The acid dissolves with evolution of heat. After a few minutes the dihydrobromide starts to separate. The mixture becomes almost solid. It is filtered after two hours, the crystals are washed with some conc'd hydrobromic acid and dried in a desiccator; yield 16–18 g., m.p. 175° (dec.).

Anal. Calc'd for $C_{18}H_{20}N_2O_4 \cdot 2HBr$ (490.22): C, 44.10; H, 4.52; N, 5.71.

Found: C, 44.90; H, 4.30; N, 6.27.

4. *Hydrogenation of dl- α,β -bis(benzylamino)succinic acid.* Six grams of *dl*- α,β -bis(benzylamino)succinic acid, 26 cc. of acetic acid, 5 cc. of hydrochloric acid (35%), and 2 g. of palladium charcoal (10% Pd) are hydrogenated at 800 lbs. pressure. The temperature is kept for 17 hours at 35°, for 6 hours at 50–60° and finally for 15 hours at 20°. The solution smells of toluene and a precipitate has formed. It is dissolved by heating to about 60° and the solution is filtered. The catalyst is washed with dilute hydrochloric acid. The combined filtrates are distilled to dryness. The residue is an amorphous yellow material which crystallizes immediately upon addition of 70 cc. distilled water. It is filtered, washed with water and alcohol, and dried. The crystals melt at 324–326° (dec.).

Anal. Calc'd for $C_{18}H_{18}N_2O_4$: C, 32.43; H, 5.44; N, 18.91.

Found: C, 31.54; H, 5.53; N, 18.41.

Benzoyl derivative. Two hundred mg. of the acid is benzoylated by shaking with 1.2 cc. of benzoyl chloride in 10 cc. of 3 *N* sodium hydroxide and 5 cc. of water. The mixture is acidified after 4 hours. The crystals are filtered, dried, and extracted with hot ligroin to remove benzoic acid. The undissolved material is crystallized from dil. acetic acid (40%). The resulting dibenzoyl compound melts at 208–210°, which is the melting point of the dibenzoyl derivative of the meso compound (9).

Anal. Calc'd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.52; N, 7.86.

Found: C, 60.51; H, 4.68; N, 8.26.

The hydrogenation of the *dl*- α,β -bis(benzylamino)succinic acid has therefore yielded meso- α,β -diaminosuccinic acid, indicating isomerization during the hydrogenation.

Acknowledgment. I am indebted to Dr. Al Steyermark for the microanalyses reported in this paper.

SUMMARY

1. An improved method for the preparation of α,β -bis(benzylamino)succinic acids is described.

2. Catalytic debenzylation of α,β -bis(benzylamino)succinic acid is a convenient method for the preparation of meso- α,β -diaminosuccinic acid.

NUTLEY, N. J.

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THE PREPARATION OF A SERIES OF 3-METHYL-5-SUBSTITUTED CYCLOHEXANONE-3-CARBOXYLIC ESTERS¹

WILLET F. WHITMORE AND CARLETON W. ROBERTS

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In connection with certain other investigations it became desirable to prepare as intermediates a series of esters of alkyl substituted cyclohexanone-3-carboxylic acids. The present report describes the preparation and properties of these intermediates.

The method adopted for the synthesis of the cyclohexanone carboxylates was based upon observations of Knoevenagel (17) and Knoevenagel and Lange (18) to the effect that 3,5-dimethyl-2-cyclohexen-1-one readily undergoes addition of sodium bisulfite in aqueous solution with the formation of 3,5-dimethylcyclohexanone-3-sodium sulfonate. Furthermore, they reported that the latter readily exchanged the sulfonate group for a cyanide group upon interaction with sodium or potassium cyanide. The resulting cyanide could be hydrolyzed with aqueous mineral acid to the corresponding 3,5-dimethylcyclohexanone-3-carboxylic acid.

It has been our experience that the hydrolysis of the cyanide and esterification of the acid can be accomplished simultaneously in methyl alcoholic sulfuric acid solution.

The reactions involved in the preparation of the esters of cyclohexanone carboxylic acids may be outlined as on page 32.

The 3-methyl-5-alkyl-2-cyclohexen-1-ones listed in table I were prepared by Knoevenagel's technique (1, 2), and have all been previously described (1, 2, 3, 4, 5, 6, 7, 8). The mechanism of the formation of 2-cyclohexen-1-ones has been discussed by Hann and Lapworth (9) and Hammett (10).

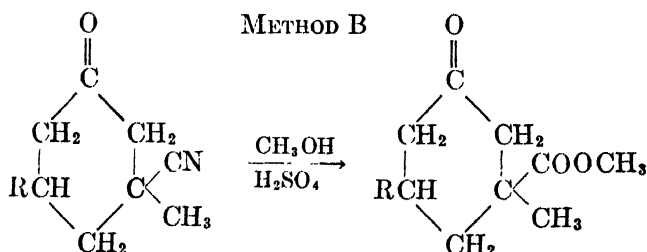
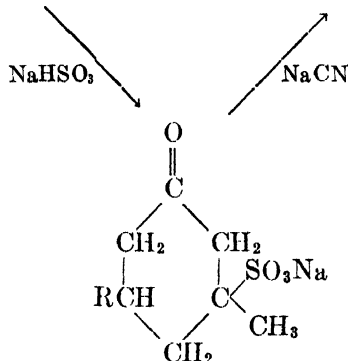
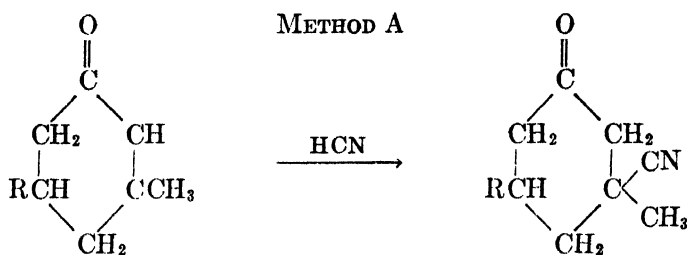
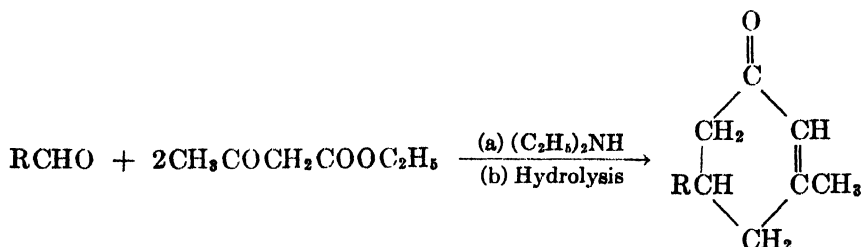
The second step involved the preparation of the 3-cyano compounds from the corresponding 3-methyl-5-alkyl-2-cyclohexen-1-ones. In addition, the preparation of 3,5,5-trimethyl-3-cyanocyclohexanone from 3,5,5-trimethyl-2-cyclohexen-1-one, isophorone, was undertaken. Presumably, these cyano ketones could be prepared by direct addition of hydrogen cyanide to the α,β -unsaturated ketone (method A) or indirectly by treatment of the addition compounds of the α,β -unsaturated ketones and sodium bisulfite with sodium cyanide (method B).

Discussion of the mechanism of direct addition of hydrogen cyanide to α,β -unsaturated carbonyl compounds may be found in the literature (9, 11, 12, 13, 14, 15).

Experiments involving direct addition of hydrogen cyanide were carried out

¹ Abstracted from a thesis presented by Carleton W. Roberts to the faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Master of Science.

by treatment of a methanol-acetic acid solution of the α,β -unsaturated ketones with an aqueous solution of sodium cyanide. Satisfactory results were obtained only in the preparation of 3,5,5-trimethyl-3-cyanocyclohexanone. Repeated attempts to prepare 3,5-dimethyl-3-cyanocyclohexanone resulted only in the

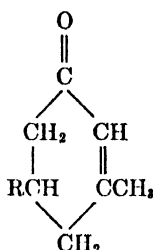


recovery of considerable amounts of unsaturated ketone, and isolation of small amounts of a mixture of the 3,5-dimethylcyclohexanone-3-carboxylic acid and amide. In the latter case it was evident that some 3-cyano compound must have been formed, but in no instance were satisfactory yields of the 3-cyano compound obtained.

Since the direct addition of hydrogen cyanide to the 3,5-dimethyl-2-cyclohexen-1-one did not give good results, the indirect method, replacement of the sulfonic acid radical in the 3 position by the cyanide group, was investigated. The preparation was carried out by boiling a mixture of the α,β -unsaturated ketone and an aqueous solution of sodium bisulfite; the reaction was considered complete when the ketone had dissolved completely and the solution became homogeneous and clear. No attempt was made to isolate these bisulfite addition compounds. They were treated *in situ* with a concentrated solution of sodium cyanide to effect conversion to the 3-cyano derivatives.

Connor (16) reviewed generally the literature concerning the replacement of the sulfonic acid grouping by cyanide, and Knoevenagel (17) and Knoevenagel

TABLE I
3-METHYL-5-SUBSTITUTED-2-CYCLOHEXEN-1-ONES



R	B P (°C)	PRESSURE (MM)	YIELD (%)	REF.
H	198-202	760	30	(3)
CH ₃	208-211	760	40	(3)
C ₂ H ₅	226-230	760	42	(4)
<i>n</i> -C ₃ H ₇	120-122	12	45	(5)
<i>i</i> -C ₃ H ₇	124-126	16		
	113-116	11.5		
	108-110	9	51	(5)
<i>i</i> -C ₄ H ₉	111-112	5		
	133-135	11	41	(2)
C ₆ H ₅	179-181	12	45.6	(2)

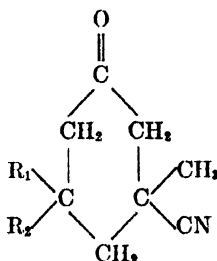
and Lange (18) prepared the 3,5-dimethyl-3-cyanocyclohexanone from the corresponding bisulfite addition compound. Except in the preparation of the 3,5,5-trimethyl-3-cyanocyclohexanone, satisfactory yields of 3-cyano compounds were obtained in all cases. Although the bisulfite addition product of isophorone apparently formed, since the ketone dissolved on refluxing in aqueous bisulfite solution, treatment of this solution with aqueous sodium cyanide resulted in almost quantitative recovery of the unsaturated ketone.

The third step in the preparation, the hydrolysis-esterification of the 3-cyano compounds to give the methyl esters of the corresponding carboxylic acids, was accomplished by refluxing a methyl alcohol-sulfuric acid solution of the cyanide for several hours and subsequent isolation and purification of the esters (19).

This⁷ procedure gave good yields except in the preparation of methyl 3-methyl-cyclohexanone-3-carboxylate. The keto esters were further characterized as 2,4-dinitrophenylhydrazones as indicated in Table III.

The authors wish to express their gratitude to Dr. Robert M. Herbst of E. Bilhuber Inc., Orange, New Jersey, for his suggestions, and interest in this work.

TABLE II
3-METHYL-5-SUBSTITUTED-3-CYANOCYCLOHEXANONES



R ₁	R ₂	FORMULA	B.P. (°C.)	PRESSURE (MM.)	M.P. (°C.)	YIELD (%)	ANAL., % N ^b	
							Calc'd	F'd
H	H	C ₈ H ₁₁ NO	92-93	2		32.1	10.2	10.1
			139-142	16				
			107-109	4				
CH ₃	H	C ₉ H ₁₃ NO	145-146	12	93-94 ^a	40.8	9.3	9.2
C ₂ H ₅	H	C ₁₀ H ₁₅ NO	132-133	3		30.0	8.5	8.5
<i>n</i> -C ₃ H ₇	H	C ₁₁ H ₁₇ NO	142-143	8		66.7	7.8	7.9
			115-116	1				
			154-156	11				
<i>i</i> -C ₃ H ₇	H	C ₁₁ H ₁₇ NO	163-166	15		32.4	7.8	7.5
			115-116	2				
			147-149	9				
<i>i</i> -C ₄ H ₉	H	C ₁₂ H ₁₉ NO	140-141	4	103-103.5	55.6	7.2	7.2
C ₆ H ₅	H	C ₁₄ H ₁₉ NO	184-186	3-5		57.0	6.6	6.5
CH ₃	CH ₃	C ₁₀ H ₁₉ NO	144-145	12		60.0	8.5	8.5

^a Knoevenagel and Lange (18) gave m.p. 92-94°.

^b Kjeldahl Analysis done by Control Laboratory of E. Bilhuber, Inc., Orange, New Jersey.

Grateful acknowledgment is made also to E. Bilhuber, Inc., in whose laboratories this work was done.

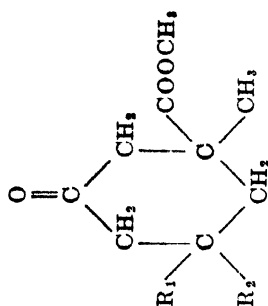
EXPERIMENTAL²

Preparation of 3-methyl-5-alkyl-2-cyclohexen-1-ones. These compounds were prepared by Knoevenagel's method (1, 2) using six moles of acetoacetic ester, three moles of freshly distilled aldehyde, and 15 cc. of either diethylamine or piperidine.³ The results of these preparations are summarized in Table I.

² All melting points and boiling points are uncorrected.

³ The initial preparations of the 2-cyclohexen-1-ones were undertaken prior to the publication of an improved synthesis (5).

TABLE III
METHYL 3-METHYL-5-SUBSTITUTED-CYCLOHEXANONE-3-CARBOXYLATES



R ₁			R ₂	CYCLOHEXANONE CARBOXYLATES					2,4-DINITROPHENYLHYDRAZONES					
				FORMULA	B P (°C)	PRESSURE (MM.)	YIELD (%)	ANAL. ^a			M.P. (°C)	FORMULA	ANAL., % N ^a	
								Calc'd	H	C			Calc'd	F'd
H	H	C ₉ H ₁₄ O ₂	128.5-130.5	15	25.0	63.5	8.2	63.8	8.2	C ₁₅ H ₁₈ N ₂ O ₆	16.0	16.0		
CH ₃	H	C ₁₀ H ₁₆ O ₂	95.6-96	1	66.5	65.2	8.7	65.1	8.8	C ₁₆ H ₂₀ N ₂ O ₆	15.4	15.5		
C ₂ H ₅	H	C ₁₁ H ₁₈ O ₂	124-125	12	72.0	66.7	9.1	66.5	9.1	C ₁₇ H ₂₂ N ₂ O ₆	14.8	14.7		
			101.5-102	1										
n-C ₃ H ₇	H	C ₁₂ H ₂₀ O ₂	104-105	1	86.7	67.9	9.4	67.9	9.4	C ₁₈ H ₂₄ N ₂ O ₆	14.3	14.1		
			149-150.5	15										
i-C ₃ H ₇	H	C ₁₂ H ₂₀ O ₂	94-95	1	83.3	67.9	9.4	68.3	9.5	C ₁₈ H ₂₄ N ₂ O ₆	14.3	14.1		
i-C ₄ H ₉	H	C ₁₃ H ₂₂ O ₂	136-140	9-10	57.7	69.0	9.8	70.7	9.7	C ₁₉ H ₂₆ N ₂ O ₆	13.8	13.8		
			131-132	8										
C ₆ H ₅	H	C ₁₄ H ₁₈ O ₂	174-176	5-6	75.0	73.1	7.4	74.5	7.3	C ₂₁ H ₂₂ N ₂ O ₆	13.1	13.3		
CH ₃	CH ₃	C ₁₁ H ₁₈ O ₂	108-109	1	65.4	66.7	9.1	67.8	9.1	C ₁₇ H ₂₂ N ₂ O ₆	14.8	15.3		
			131-134	12										
			136-137	13										

^a Microanalysis for Carbon Hydrogen and for Nitrogen by W. Saschek New York, New York.

3,5,5-Trimethyl-2-cyclohexen-1-one, obtained from the Carbide & Carbon Chemical Corporation, was redistilled, b.p. 212–214°.

Preparation of the 3-cyano compounds. Method A (Direct). One hundred thirty-eight grams (1 mole) of isophorone (b.p. 212–214°) was dissolved in a mixture of 950 cc. of methanol, 50 cc. of water, and 60 g. (57.2 cc., 1 mole) of glacial acetic acid. To this was added during 15 minutes, with constant stirring, 98 g. (2 moles) of powdered sodium cyanide dissolved in 375 cc. of water. The resulting warm solution was allowed to stand for one week at room temperature.

After removal of most of the methanol from the reaction mixture under reduced pressure (water-bath temperature between 50–60°), the residual solution was diluted with 500 cc. of water, and the oil taken up in 250 cc. of benzene. Since some solid separated on shaking with benzene, it was found helpful to filter the benzene layer and the interfacial layer after most of the clear aqueous layer had been drawn off. The aqueous layer was extracted with two 200-cc. portions of benzene, the benzene solutions combined, and dried over sodium sulfate.

Most of the benzene was removed by distillation at atmospheric pressure, and the residual material was distilled under reduced pressure. The fractions shown in Table IV were obtained.

TABLE IV
FRACTIONATION OF 3-CYANO COMPOUND

FRACTION	B.P. (°C)	BATH TEMP. (°C)	PRESSURE (MM.)	YIELD	PRODUCT
1	92–100	120–140	11–14	38 g.	isophorone
2	120–140	140–160	11	20 g.	mixed
3	144–150	174–178	11	71 g.	cyanide

The third fraction solidified on cooling and was practically pure cyanide.

A portion was recrystallized from 99% isopropyl alcohol, m.p. 69.5–70.5°.

Method B (Indirect). The cyclohexenone (0.25 mole) was suspended in a solution of 34.5 g. (0.31 mole) of sodium bisulfite and 75 cc. of water, and boiled under reflux until the ketone dissolved completely (20–30 minutes). The solution was cooled, and a warm solution of 15.2 g. (0.31 mole) of sodium cyanide in 35 cc. of water was added. While the reaction mixture was heated for an hour in a boiling water-bath, some solid material separated, and the cyano ketone appeared as an immiscible oil. The reaction mixture was cooled, the oil taken up in 50 cc. of benzene, and the aqueous solution and solid extracted with two 50-cc. portions of benzene. The benzene extracts were combined and dried over sodium sulfate.

After removal of most of the benzene at atmospheric pressure, the residual material was distilled under reduced pressure. Three fractions were collected. The first fraction was original ketone, the second fraction was a mixture of the ketone and cyano ketone, and the third fraction was practically pure cyano ketone. The yields, allowing for recovered unsaturated ketone, varied between 30% and 70% with the exception of the 3,5,5-trimethyl-2-cyclohexen-1-one which gave no cyano compound by this method. The cyano compounds were purified either by redistillation or, in the case of solids, by recrystallization from 99% isopropyl alcohol. The main cyanide fraction was generally employed in the next step without further purification. The results of methods A and B are summarized in Table II.

Hydrolysis and esterification of cyanides. One mole of the cyano ketone was suspended in a carefully prepared solution of two moles of concentrated sulfuric acid in an equal weight of 95% methyl alcohol. After standing overnight, the reaction mixture was boiled

under reflux for about seven hours. After about three and one-half hours the reaction mixture separated into two phases and enough methanol (75-100 cc.) was added carefully to restore a homogenous solution. Finally the reaction mixture was cooled and poured into about a liter of cold water. The ester separated and was taken up in about 200 cc. of benzene. The aqueous portion was extracted with two 200-cc. portions of benzene. The benzene solutions were combined, washed with a 10% solution of potassium carbonate, and dried over anhydrous sodium sulfate.

After the solvent was removed from the benzene solution at atmospheric pressure, the ester was distilled under reduced pressure.

The yields varied between 25-86% of water-white oily products which usually turned darker on standing in the light or on storage. Analytical samples were purified by repeated redistillations; analytical results indicated that the products were the desired keto esters. The results are summarized in Table III.

Preparation of 2,4-dinitrophenylhydrazones of keto esters. The 2,4-dinitrophenylhydrazones were prepared in the usual manner (20) except that methyl alcohol was used in place of ethyl alcohol. Their properties are recorded in Table III.

SUMMARY

1. Using Knoevenagel's methods, a series of 3-methyl-5-R-2-cyclohexen-1-ones, where R was hydrogen, methyl, ethyl, *n*-propyl, isopropyl, isobutyl, or phenyl, has been prepared.

2. The 3-cyanocyclohexanones were prepared from these unsaturated ketones and isophorone and their properties described. It was found that the cyano compound could be prepared best in two stages, (a) the addition of sodium bisulfite to the unsaturated ketone, and (b) replacement of the sulfonate group by the cyanide group except in the case of 3,5,5-trimethyl-3-cyanocyclohexanone, which could be prepared only by direct addition of hydrogen cyanide to the unsaturated ketone.

3. The 3-methyl-5-R-3-cyanocyclohexanones were converted by one step hydrolysis-esterification to the corresponding methyl 3-methyl-5-R-cyclohexanone-3-carboxylates. The 2,4-dinitrophenylhydrazones of this series of methyl 3-methyl-5-R-cyclohexanone-3-carboxylates were prepared.

BROOKLYN, NEW YORK

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IDENTIFICATION BY DISTRIBUTION STUDIES. IX. APPLICATION TO METABOLIC STUDIES OF 4-AMINOQUINOLINE ANTIMALARIALS¹

ELWOOD O. TITUS, LYMAN C. CRAIG, CALVIN GOLUMBIC, HAROLD R. MIGHTON, IRIS M. WEMPEN, AND ROBERT C. ELDERFIELD

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Although the capacity of the animal organism for causing transformations of drugs has been recognized, many studies of the pharmacological or therapeutic activities of various substances appear in which this factor has not been taken into consideration. Thus frequently, the observed effect has been related to the dosage of a given drug or to drug levels in various parts of the body as determined spectrophotometrically. By the latter method, confusion may occur between the identification of the drug administered and metabolic products of the drug which, while actually being the active agent or agents, still show spectrographic properties closely similar to the drug itself. Often this has been the only feasible approach because of the difficulty in the detection, isolation and identification of the small amounts of the transformation products carried in the complicated mixture present in the biological fluids. The need for such information, often realized in the past, is obvious for the proper evaluation or interpretation of the underlying cause of the desired effect.

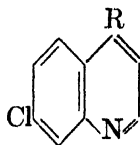
The method of counter-current distribution (1) is an approach which should prove helpful for the problem as stated, because of the quantitative nature of the process and other advantages mentioned in previous publications (2). An excellent opportunity to test this thesis came with the appraisal of the 4-aminoquinoline group of drugs as among the most effective suppressive antimalarials, and the need for knowledge of the fate and physiological disposition of representative members of the series. It was thought that information on the mechanism of detoxification of the drugs could prove of value both as a guide to more efficient administration of the substances and as a source of leads for the synthesis of perhaps even more highly useful drugs.

In the present investigation, the metabolic fate of three typical 4-aminoquinolines as indicated by the nature of the degradation products isolated from the urine of normal human volunteers receiving the drugs has been the subject of a preliminary study. Unfortunately, termination of hostilities prevented accumulation of sufficient material to enable the studies to be carried as far as might have been desired. The drugs investigated were 4-(4-diethylamino-1-methylbutylamino)-7-chloroquinoline (chloroquine) (SN-7618) (I),² 4-(3-di-

¹ The work described in this paper was done in part under contracts, recommended by the Committee on Medical Research, between the Rockefeller Institute for Medical Research and Columbia University, and in part under a grant from the United States Public Health Service (National Institute of Health) to Columbia University.

² The prefix, SN, identifies a drug in the "Survey of Antimalarial Drugs," Edwards Bros., Ann Arbor, Mich., 1946. The numbers will be used frequently for convenience hereinafter.

ethylamino-2-hydroxypropylamino)-7-chloroquinoline (oxychloroquine) (SN-8137) (II) and 4-(3-diethylaminopropylamino)-7-chloroquinoline (SN-9584) (III).



- I. $R = \text{NHCH}(\text{CH}_3)(\text{CH}_2)_3\text{N}(\text{C}_2\text{H}_5)_2$ (SN-7618)
- II. $R = \text{NHCH}_2\text{CH}(\text{OH})\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ (SN-8137)
- III. $R = \text{NH}(\text{CH}_2)_3\text{N}(\text{C}_2\text{H}_5)_2$ (SN-9584)
- IV. $R = \text{NHCH}(\text{CH}_3)(\text{CH}_2)_3\text{NHC}_2\text{H}_5$ (SN-13,616)
- V. $R = \text{NHCH}_2\text{CHOHCH}_2\text{NHC}_2\text{H}_5$
- VI. $R = \text{NH}(\text{CH}_2)_3\text{NHC}_2\text{H}_5$ (SN-13,588)

Since the potentialities of the method of counter-current distribution had been but incompletely explored at the time this investigation was begun, a preliminary part of the present work involved a study of the most efficient means of applying the procedure to the two types of mixtures encountered, *i.e.* mixtures of typical quinoline bases extractable from urine with chloroform, and mixtures of water-soluble amphoteric substances extractable with butanol.

At the outset the method was subjected to a critical test in which the homogeneity of the drugs administered as determined by the counter-current technique was checked against the homogeneity as determined by the solubility method of Northrup and Kunitz (3).³ The latter method appeared to be the most suitable of the methods previously available for determining purity, and also offered certain theoretical advantages as a test of the sensitivity of the distribution process. By such a check of the purity of the original drugs, the possibility of the appearance of degradation products as artifacts was eliminated.

In analysis by distribution, a mixture is subjected to a series of stepwise extractions between portions of two immiscible solvents moving counter-currently. Components, the higher partition coefficients of which favor concentration in the upper layer, will naturally move more rapidly through the apparatus in the direction in which this phase is traveling, so that after a time the several substances in a mixture appear as isolated bands moving through the apparatus at different rates in a manner somewhat analogous to the spreading of bands on a chromatographic column. Each operation in which the two phases are equilibrated, allowed to settle, and transferred to new positions is termed a plate, in view of the analogy with other counter-current fractionation processes. After a suitable number of plates have been applied, the contents of each tube are analyzed, and the concentrations plotted as a function of the position of the tube in the apparatus. The stepwise nature of the procedure has made possible a

³ A detailed and rigorous comparison of the two methods will appear shortly. Craig and co-workers, in press.

simple mathematical treatment which permits the calculation of theoretical distribution curves for pure substances as a function of their distribution constants (1, 4). This has enhanced the usefulness of the technique as a means of estimating homogeneity, since the quantity of impurity may be estimated by summation of the differences between the theoretically and experimentally obtained ordinates of a distribution curve. When, as in these determinations, the two substances are separated more or less completely, the relative amounts of the components of the mixture can be estimated by summation of the ordinates in each band.

The usefulness of the technique obviously depends on the extent to which the components of a mixture differ in distribution constant, and upon the availability of a suitable analytical method which will reveal all the impurities, so that it seemed desirable to check the results by an independent method.

Such a method is available in the Northrop and Kunitz technique in which a series of samples of increasing weight are equilibrated with a fixed volume of solvent, and the concentrations of the resulting solutions are plotted against sample weight. It follows from the phase rule that, for a pure substance, such a curve should rise at a 45° slope from the origin provided the ordinates are properly chosen, indicating complete solution of the sample, until at the saturation point it becomes a horizontal straight line, indicating the constant solubility of a pure substance. With a mixture, the first break in the rising curve occurs when the solution becomes saturated with one component. The curve then rises at a lesser slope, becoming horizontal only when sufficient quantity of sample is taken to saturate the liquid phase with all of the components of the mixture. Determination of the samples and concentrations by weight makes the results independent of any particular analytical method, and, except in the improbable instance of two components with identical solubilities, any type of mixture should be revealed.

When samples of the three drugs were compared by the two methods, the quantity of impurity, estimated in terms of equivalents of acid required by titration of the contents of each tube of the Craig apparatus, was found to be consistently a little higher than the amount revealed by the solubility technique. The results were of the same magnitude, and in no case was there sufficient impurity to cast doubt on the relationship between degradation products and starting materials.

The efficient separation of small quantities of impurities from the drugs in the homogeneity studies encouraged the use of the same two phase systems of organic solvents and concentrated buffers for the isolation of degradation products, since it appeared that molecules with but minor structural differences might differ widely in distribution constants in such systems. This follows naturally from the nature of the equilibria involved. The over-all partition coefficient which determines the behavior of a substance on distribution may be considered to result from the contributions of several equilibria: the distribution of the free base between solvent and aqueous phase; the molecular association, if any, of the compound in the buffer or organic solvent; and the ionization of the base in the

aqueous phase (2). The ionization constant determines the percentage of the base existing in the ionic form in the aqueous phase. By fixing the pH with buffer an over-all partition ratio in the vicinity of one can be obtained. Within this range the distribution constant changes rapidly with pH; and conversely, in systems buffered to constant pH, structural changes which affect pK_a values should have decided effects on distribution constants. This has proved to be the case with the drugs and their degradation products encountered in this investigation as well as with numerous other quinoline bases examined by this technique, details of which have been reported elsewhere (5). From experience to date, the conclusion appears justified that for substances of this type, the distribution constant in a well-defined system of buffer and solvent can be safely regarded as a characteristic physical constant.

With the fundamental reliability of the counter-current method apparently established for the separation of mixtures of the type likely to be encountered, attention was turned to the problem at hand. The collected urine of the volunteers was made ammoniacal and extracted with chloroform and the quinoline bases obtained. The amounts thus secured accounted for about 40% of the drug administered in the case of SN-7618, 50% of the administered SN-8137 and 15% of the administered SN-9584 on the assumption of an output of one liter of urine per day per subject.

As pointed out by Craig (2), counter-current distribution is most efficient when the partition coefficient between the two phases is unity. Therefore systems of organic solvent and buffer between which the components of the mixtures of degradation products extracted with chloroform distributed equally were chosen. The contents of the tubes were analyzed spectrophotometrically by measuring the optical density of the solutions at 330 m μ , at which point a characteristic maximum of derivatives of 4-amino-7-chloroquinoline occurs. The complete absorption curve for SN-7618 has been reported by Drake and co-workers (6). None of the substances isolated from this chloroform extractable fraction showed significant deviations from this characteristic absorption curve.

Distribution of the chloroform extractable mixtures from the urine of subjects receiving each of the three drugs resolved each into two fractions, one the recovered starting material, and the other, a degradation product which proved in each case to be the monoethylamino compound (IV, V, VI) resulting from the loss of one ethyl group from the terminal diethylamino group of the side chain. De-ethylation, apparently a general detoxification mechanism for this class of compound, has not been frequently observed in the cases of other substances, although it has been noted with N-ethylglycine (7) and with N-ethylbarbital (8). Oxidation of the 2-position of the quinoline nucleus to yield the carbostyryl, which might have been expected in the light of the data of Mead and Koepfli (9) concerning the degradation of quinine, was not observed. The extent of de-ethylation was found to vary with the side chain; the monoethyl compound accounted for roughly 25% of the chloroform extractable bases from urine in the case of SN-7618, 60% with SN-8137, and 20% with SN-9584.

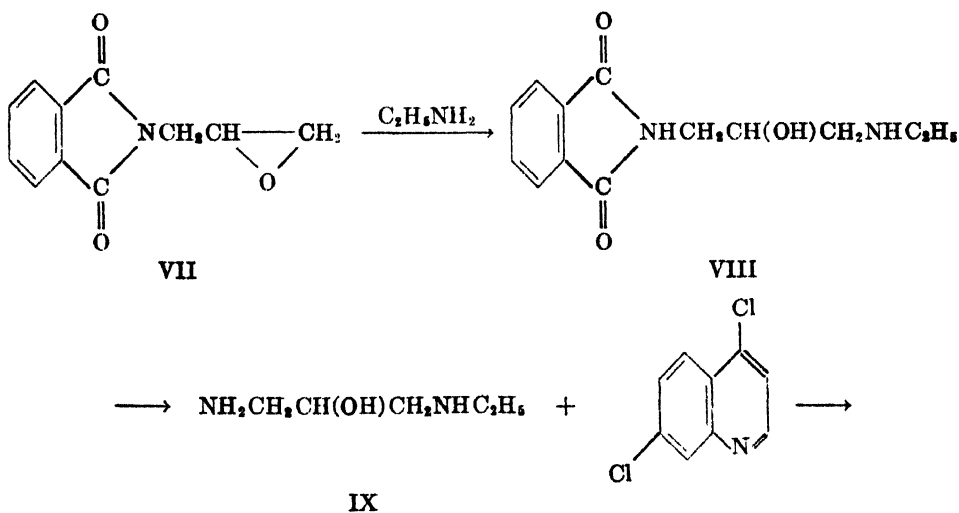
In only one instance was a degradation product other than the de-ethylated

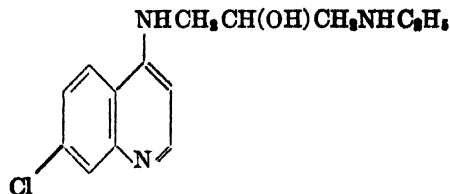
compound isolated from the chloroform extracts. Occasional batches of urine from subjects receiving SN-9584 contained a high-melting substance, which appeared in the same fraction as the monoethyl compound, VI. Although difficultly separable by distribution, the two were readily separated by fractional crystallization. Analytical data suggested the possibility of a hydrated hydroxylamine derivative of the monoethyl compound, VI, and the absorption spectrum indicated that the quinoline nucleus had not been modified. Unfortunately, the few urine specimens in which this compound was found provided only enough for the analytical data and it was not definitely identified.

Although both SN-7618 and SN-8137 contain asymmetrical carbon atoms, only in the case of the former was there evidence of preferential degradation of one isomer.

On the basis of the above information, particularly the indication from N-ethyl determinations that the three degradation products were indeed the substances represented by IV, V, and VI, *dl*-4-(4-ethylamino-1-methylbutylamino)-7-chloroquinoline (IV) (SN-13,616) and 4-(3-ethylaminopropylamino)-7-chloroquinoline (VI) (SN-13,588) were synthesized elsewhere (10, 11). 4-(3-Ethylamino-2-hydroxypropylamino)-7-chloroquinoline (V) has been synthesized in the course of the present work. Final identification of the degradation products with the synthetic substances was on the basis of distribution constants and mixed melting points in the cases of V and VI. In the case of IV, the preponderance of an optical isomer in the degradation product rendered the melting points of little use, although the agreement of the distribution constants was satisfactory.

For the synthesis of the monoethyl compound, V, reactions VII-V were used. Epoxypropylphthalimide (VII) (12) was treated with ethylamine to yield 1-ethylamino-2-hydroxy-3-phthalimidopropane (VIII) which was hydrolyzed to 2-hydroxy-3-ethylaminopropylamine (IX). The latter was condensed with 4,7-dichloroquinoline according to the general method of Pearson, Jones, and Cope (13) to yield the monoethyl compound, V.





V

The behavior of SN-13,616 and SN-13,588 in the human furnished interesting confirmation for the evidence here presented that these two substances represent at least one possible mode of elimination of the two parent drugs, SN-7618 and SN-9584. Although both monoethyl derivatives showed a high order of activity against avian malaria,² absorption studies showed that both drugs were poorly absorbed in man and eliminated unchanged to a great extent (14).

After removal of chloroform extractable degradation products from the ammoniacal urine of subjects receiving SN-8137 and SN-9584, further extraction of the urine with butanol yielded a series of more water-soluble degradation products. Separation of these substances from the urea and other constituents of normal urine was partially achieved by cautious addition of chloroform to methanolic solution of residues from the butanol extract. The mother liquors remaining after the separation of the urea were evaporated and the residues fractionated further by distribution.

The slight solubility in ordinary organic solvents of these amphoteric substances limited the solvent pairs in which distribution was practical to systems of highly polar solvents such as butanol and water. The necessity of recovering distributed material by evaporation of both upper and lower phases made the use of buffers impractical if contamination of the products with salt was to be avoided. Despite the fact that these restrictions appeared to eliminate many of the factors which made the distribution constants of related substances more sensitive to differences in structure, it was possible to achieve efficient separation of the degradation products by taking advantage of their amphoteric properties and distributing them first in butanol and dilute ammonia and subsequently in butanol and dilute acetic acid.

Use of the first system served chiefly to remove contaminants since distribution of the products of either drug yielded similar patterns. These revealed two main fractions, one a band of material of low distribution constant containing about 80% of the total solids, and the other, a fraction near the center of the distribution curve in which were concentrated most of the substances the absorption of which at 330 $m\mu$ indicated their quinoline nature. This central fraction was redistributed in the second pair of solvents, butanol and 10% acetic acid, which proved to be most effective for the separation of the quinoline derivatives from each other. The distribution curves obtained with this system revealed the strong influence of the nature of the side chain on the mode of elimination of the 4-aminoquinolines.

The hydroxylated side chain of SN-8137, which renders possible the formation

of water-soluble conjugates, apparently favors elimination of the drug as a uronide, possibly a glucuronide, largely to the exclusion of further degradation. Such a uronide, which was found by the butanol-acetic acid distribution to account for the major part of the material extracted from the urine by butanol, was freed from non-quinoline contaminants by repeated redistributions and finally obtained as an amorphous solid. Analytical data suggested the formulation of this substance as a uronide of the N-oxide of the original drug, and the behavior of its hydrolysis products suggested that the conjugate was more than a simple glucuronide of the original drug. Optimal acid hydrolytic conditions were established by counter-current distribution of the reaction products from several runs made under increasingly severe conditions. The mildest conditions which gave complete conversion of the uronide from the water-soluble derivative to a chloroform-soluble base were thereafter used. This acid hydrolysis split the compound into water-soluble material which gave naphthoresorcinol color reactions typical of uronic acids, and a chloroform-soluble base, the absorption spectrum and behavior of which upon distribution in solvent-buffer systems were identical with those of the pure drug SN-8137. However, when an attempt was made to distill this chloroform-soluble base, extensive decomposition occurred in contrast to the behavior of SN-8137 on distillation. Likewise the picrate prepared from the base was a mixture from which, after reduction, the characteristic stubby rods of the picrate of SN-8137 could be separated from a picrate crystallizing as thin needles by fractional crystallization. Apparently the quinoline compounds originally present in the conjugate consisted of a mixture of conjugates of SN-8137 and a closely related substance. In the light of the experience with the oxygenated derivative of the de-ethylated SN-9584, which was difficult to separate from the parent compound by distribution, this might be the N-oxide.

The second fraction, which appeared in small amounts in the same butanol-acetic acid distribution as the conjugate, yielded a small amount of crystalline product melting at 163–165°. This was obtained in too small a quantity for analysis.

Much more extensive degradation was revealed when the butanol extractable quinolines from the degradation products of the relatively simple diethylamino-propylamino quinoline (SN-9584) were distributed in the butanol-acetic acid system. Three major fractions were observed, but crystalline material was obtained from only one. The fraction which appeared in the same region of the distribution as had the conjugate of SN-8137 was not obtained pure. It appeared to have suffered alteration of the quinoline nucleus, as the typical absorption spectrum was distorted. It was not a conjugate of the original drug, since no chloroform-soluble material could be obtained after prolonged hydrolysis.

A second fraction appearing in the center of the distribution curve was isolated by repeated redistribution and recrystallization from water, and identified as N-(7-chloroquinolyl-4-)- β -alanine, a product to be expected from the oxidative deamination of the side chain. This compound was readily prepared by con-

densation of 4,7-dichloroquinoline with β -alanine in phenol solution. At the same time the next lower homolog was similarly prepared from glycine in the hope that it might prove to be identical with the material which melted at 163–165° isolated from the degradation products of SN-8137. However, N-(7-chloroquinolyl-4-)-glycine decomposed at 251–253°.

Both acids were characterized by methylation with diazomethane, which yielded the methyl ester of the betaine in each case, in agreement with the observations of Kuhn and Brydowna on the methylation of zwitterions with this reagent (15).

EXPERIMENTAL^{4, 5, 6}

Homogeneity of the drugs and test of the counter-current method. (a) *Use of the solubility method.* Samples of SN-7618, SN-8137, and SN-9584 as the diphosphates were examined by the method of Northrop and Kunitz (3). A series of samples ranging from 20 to 300 mg. was equilibrated at 0° for twenty-four hours with 3 ml. of solvent in an apparatus similar to that of Ing and Bergmann (16) and Moore and Stein (17). The solubility was determined by weighing the residue after centrifuge filtration and the per cent of impurity was estimated from the slope of the curve obtained by plotting solubility in mg. per ml. versus the weight of the original sample. A representative curve obtained with SN-7618 is shown in the top part of Figure 1 and the data obtained with all three drugs are summarized in Table I.

(b) *Use of the counter-current method.* Samples of approximately 100 mg. of the same drugs were subjected to "counter-current distribution" between chloroform and 2 molar phosphate buffers in a 20-tube Craig apparatus (2). Upon completion of the distribution, the aqueous layer of each tube was made alkaline with sodium hydroxide and the organic bases were extracted by shaking into the chloroform phase, which was then separated. Three milliliters of water was added to each chloroform solution and the quantity of base in each tube was estimated by titration of the chloroform-water mixture with 0.1 *N* hydrochloric acid using sodium alizarin sulfonate as indicator. The mixture was agitated for twenty to thirty seconds after each addition of acid to ensure complete extraction of base into the aqueous phase containing the indicator. The number of mls. of hydrochloric acid required for the titration of each tube was plotted against the tube number. The two maxima in the resulting distribution curve indicated the separation of a small quantity of contaminant from the main body of the material.⁷ The sums of the ordinates of the points within the two parts of the curve were taken as a measure of the relative amounts of drug and contaminant.

Typical data obtained by the two methods with a sample of SN-7618 are compared in Fig. 1 and the results for all three drugs are summarized in Table I. The inhomogeneity present as indicated by the counter-current method was consistently slightly higher (0.5%) than that indicated by the solubility method. This deviation was not sufficiently large to interfere with the later use of the former method.³

⁴ Except where otherwise noted, the experiments were carried out in the laboratories of the Rockefeller Institute for Medical Research.

⁵ All melting points were taken on a heated stage microscope.

⁶ Microanalyses were done by Mr. D. Rigakos.

⁷ All distribution curves are plotted to show the fractions of higher distribution constant at the right. In all cases the sample was first added to the tube numbered 0, but since distribution is effected by transfer of the upper layers in the Craig apparatus and by the lower layers in separatory funnels, it is necessary to number the curves in opposite directions in order for curves obtained by the two techniques to be comparable.

Isolation of the degradation products of 4-(4-diethylamino-1-methylbutylamino)-7-chloroquinoline (SN-7618). (a) *Recovery of undegraded drug.* Three-liter batches of the pooled urine of normal human volunteers receiving 400 mg. per day of SN-7618 were made ammoniacal and extracted with 2 one-liter portions of chloroform. The combined chloroform

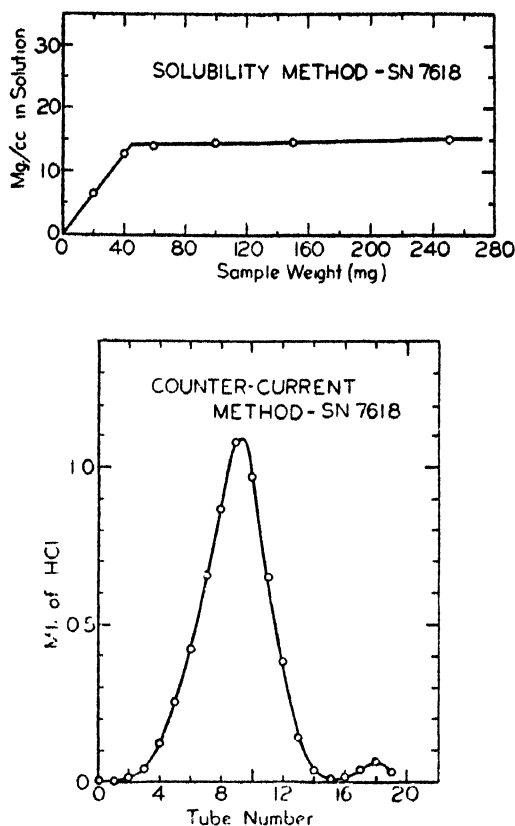


FIG. 1

TABLE I
COMPARATIVE INHOMOGENEITY DETERMINATIONS

DRUG	SOLUBILITY METHOD		COUNTER-CURRENT METHOD	
	Solvent	% Inhomogeneity	pH	% Inhomogeneity
SN-7618	Acetone-water 1:1	1.6	6.55	2.6
SN-8137	Ethanol-water 2:1	0.4	6.70	1.0
SN-9584	Acetone-water 1:2	0.2	6.70	0.5

extracts were then extracted with 250 ml. of 1.0 *N* sulfuric acid, the acid solutions were made ammoniacal, and the quinoline bases were removed by extraction into fresh chloroform. Evaporation under vacuum of the extracts yielded from 85 to 100 mg. of an oil per liter of urine. This was further fractionated by counter-current distribution between 8-ml. layers of chloroform and 2-molar phosphate buffer of pH 6.36 in a 25-tube Craig apparatus. Upon completion of the distribution, each tube of the machine was emptied into a separatory

funnel and the material from both phases concentrated into the chloroform layer by the addition of alkali and shaking. The optical density of each chloroform solution at 330 $m\mu$ was measured with a Beckman quartz spectrophotometer using a 1-cm. cell and plotted as a function of the number of the tube (Curve 1, Fig. 2).

The absorption curve of the material in the tubes containing the larger fraction, about 50% of the total, in tubes 6 to 15 of Fig. 2, proved identical with that of the original drug. The value of 0.71, calculated from Fig. 2, Curve 1 by the method of Williamson and Craig (4), for the coefficient of distribution between chloroform and the 6.36 pH buffer was in good agreement with the value of 0.70 observed with authentic SN-7618 in the same system.

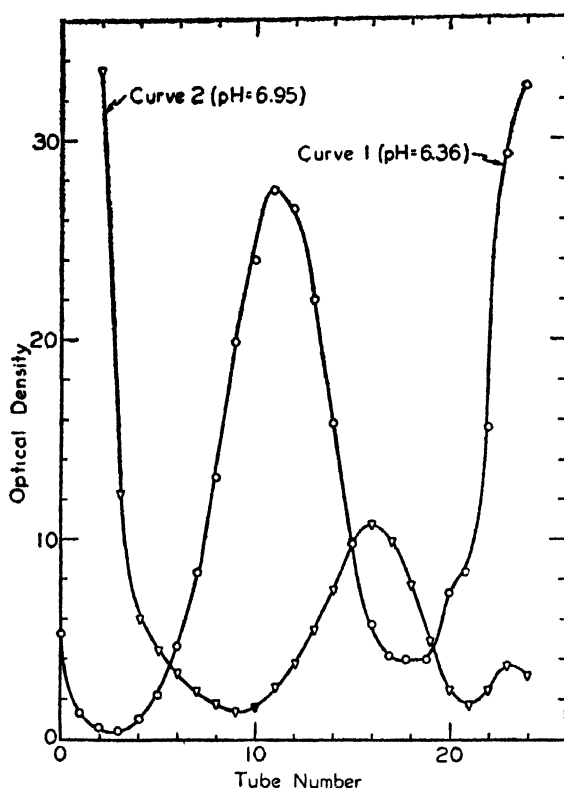


FIG. 2. DISTRIBUTION OF CHLOROFORM-EXTRACTABLE DEGRADATION PRODUCTS OF SN 7618 IN CHCl_3 AND 2-MOLAR PHOSPHATE

A sample of 70.7 mg., obtained by evaporation of several of the more concentrated chloroform solutions, melted at 83–89°. Recrystallization from ether yielded 14 mg. melting at 85–90°. A mixed melting point with a sample of the original drug (base) melting at 88–90° was 87.5–90°. The material showed slight optical activity, $[\alpha]_D^{25} + 7.5^\circ$, ($c = 0.015$ in chloroform).

Anal. Calc'd for $\text{C}_{18}\text{H}_{26}\text{ClN}_3$: C, 67.6; H, 8.2.

Found: C, 67.8; H, 8.3.

(b) *Isolation of the monoethyl compound, IV.* Another aliquot of the same material, the distribution of which was illustrated in Fig. 2, (Curve 1) was similarly distributed in chloroform and a 2 molar phosphate buffer of pH 6.95. An optically active base amounting to roughly 25% of the total material was isolated by evaporation of the solutions in tubes 13 to 18 of Fig. 2 (Curve 2). Redistribution of the material in the same system indicated

homogeneity, the partition coefficient being 1.7 as compared with the value of 1.5 observed with an authentic sample of 4-(4-monoethylamino-1-methylbutylamino)-7-chloroquinoline (10) (SN-13,616) (IV).

Molecular distillation at a bath temperature of 130° and 0.05 mm. yielded a clear distillate which slowly solidified on standing and melted at 80–95°; $[\alpha]_D^{25} +145^\circ$, ($c = 0.0145$ in methanol). The absorption spectrum in chloroform was identical with that of the original drug.

Anal. Calc'd for $C_{16}H_{22}ClN_3$: C, 65.7; H, 7.6; N, 12.1.

Found: C, 65.3; H, 7.9; N, 12.1.

An authentic sample of SN-13,616 was distilled in the same manner as the degradation product to yield a distillate which crystallized on standing and melted at 95–100°. A mixed melting point with the degradation product was 85–100°.

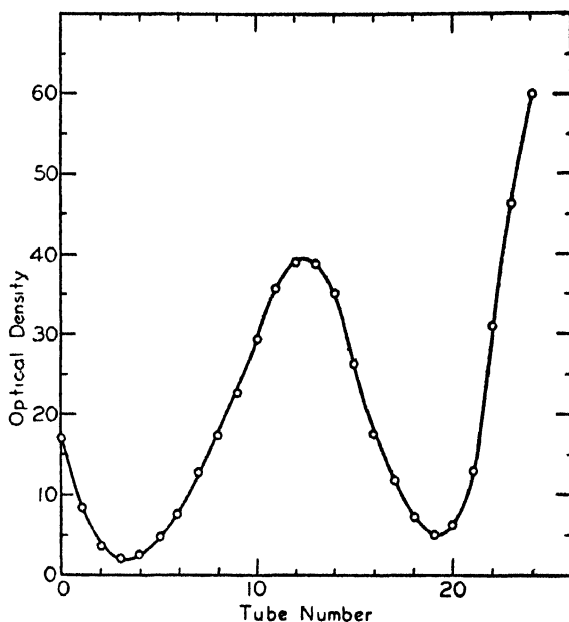


FIG. 3. DISTRIBUTION OF $CHCl_3$ -EXTRACTABLE DEGRADATION PRODUCTS OF SN 8137 IN $CHCl_3$ AND 2-MOLAR PHOSPHATE (pH = 6.70)

A dipicrate of the degradation product prepared in acetone and recrystallized from the same solvent melted at 123–133°, then resolidified at 143–158°, and finally melted at 203–206°.

Anal. Calc'd for $C_{25}H_{28}ClN_9O_{14}$: C, 44.8; H, 3.8.

Found: C, 45.2; H, 4.0.

A dipicrate similarly prepared from the authentic sample melted at 120–130°.

Anal. Found: C, 45.0; H, 4.0.

Although direct identification of the degradation product with SN-13,616 was rendered difficult because of the appearance of optical activity, a comparison of the N-ethyl values obtained with SN-7618 and the degradation product support the interpretation given. This determination commonly gives consistently low results, but the comparative figures are significant.

Anal. Calc'd for $C_{18}H_{26}ClN_3$ (SN-7618): C_2H_5 , 18.2. Found: C_2H_5 , 10.9.

Calc'd for $C_{16}H_{22}ClN_3$ (degradation product): C_2H_5 , 10.0. Found: C_2H_5 , 6.0.

Isolation of the degradation products of 4-(3-diethylamino-2-hydroxypropylamino)-7-chloro-

quinoline (SN-8137). (a) *Recovery of undegraded drug.* Urine from subjects receiving 400 mg. per day of SN-8137 was extracted as described above to yield from 100 to 130 mg. of oily residue per liter of urine. A 24-plate distribution with chloroform and a 2-molar phosphate buffer of pH 6.70 separated two fractions as illustrated in Fig. 3. The unchanged drug was recovered as an oil upon evaporation of the solutions in tubes 9 to 16 of Fig. 3. A dipicrate could be prepared in acetone in nearly quantitative yield. The melting point, 222–224°, was not depressed upon mixture of the material with the dipicrate prepared from authentic SN-8137 which also melted at 222–224°.

Anal. Calc'd for $C_{22}H_{22}ClN_2O_{11}$: C, 43.8; H, 3.7.

Found: C, 43.6; H, 3.5.

(b) *Isolation of the monoethyl compound (V).* The monoethyl compound, which comprised about 60% of the total oil obtained above, crystallized readily in rosettes of short stout needles upon evaporation of tubes 22–24 of Fig. 3. This substance melted at 178–180° and the mixed melting point with a synthetic sample of 4-(3-ethylamino-2-hydroxypropylamino)-7-chloroquinoline, melting at 178–179°, was 178–180°.

The dipicrate crystallized from acetone in compact plates, melting at 231–235°.

Anal. Calc'd for $C_{23}H_{24}ClN_2O_{11}$: C, 42.4; H, 3.3.

Found: C, 42.6; H, 3.4.

Synthesis of 4-(3'-ethylamino-2'-hydroxypropylamino)-7-chloroquinoline: (Columbia).

(a) *Epoxypropyl phthalimide.* A mixture of 100 g. of potassium phthalimide and 200 ml. of epichlorohydrin in a flask equipped with stirrer and reflux condenser was heated in a bath warmed to 160° for eight hours, during which the original pasty yellow mass was gradually transformed into a suspension of finely divided powder in dark brown liquid. Longer heating had no appreciable effect on the yield. The epichlorohydrin was distilled from the reaction mixture under water-pump vacuum, and the residue was taken up in 400 ml. of hot ethanol. The insoluble inorganic residue was filtered from the hot solution by suction and washed with 100 ml. of hot ethanol. When cooled, the combined ethanol solutions deposited 120 g. of white crystalline epoxypropylphthalimide, m.p. 89–92.5°. Recrystallization from 100 ml. of ethanol yielded 72 g. (63%) m.p. 96–98°. Weizmann and Malkowa, who prepared the substance from the bromohydrin, give the m.p. as 93–94° (12).

(b) *N-ethyl-1,3-diamino-2-propanol.* Fifty grams of epoxypropylphthalimide was added over a period of fifteen minutes to 500 ml. of a cold (–5°), vigorously stirred 33% solution of ethylamine in water. The mixture was stirred for one hour at 0 to –5°, allowed to stand for twenty hours at 10°, and then concentrated under vacuum on the steam-bath to a volume of 100 ml. after which 150 ml. of hydrochloric acid (sp. gr. 1.19) was added, and the solution was gently refluxed for two hours.

After cooling, the precipitate of 33.2 g. of phthalic acid was filtered off by suction and washed once with a little cold water. The filtrate and washings were evaporated under vacuum to less than 100 ml., cooled, and filtered free of a further small precipitate of phthalic acid. The filtrate was made alkaline with 6 N sodium hydroxide, evaporated nearly to dryness, and taken up in absolute ethanol. The alcoholic solution was filtered free of salts and evaporated under vacuum to a thick oil which was distilled through a 15-cm. Vigreux column. A considerable amount of resinous material proved undistillable; 5.65 g. (23%) of distillate, b.p. 117–119° at 18 mm., was obtained. Since further purification of the hydroxy amine by repeated distillations did not prove satisfactory, it was used directly as obtained for the subsequent step.

(c) *4-(3'-Ethylamino-2'-hydroxypropylamino)-7-chloroquinoline (V).* A mixture of 4.0 g. of once-distilled N-ethyl-1,3-diaminopropanol-2 and 6.80 g. of 4,7-dichloroquinoline (18) was heated according to the procedure of Pearson, Jones, and Cope (13). An exothermic reaction began when the bath temperature reached 148°, and the temperature of the reaction mixture rose rapidly to 160°. It was quickly cooled and maintained at 125–135° for two hours. The brittle solid reaction product was pulverized, triturated with several 100-ml. portions of ether to remove unreacted dichloroquinoline, and taken up in 30 ml. of hot

ethanol. The alcoholic solution was made alkaline with sodium hydroxide and gradually diluted with an equal volume of water. The red oil which separated from the solution was removed, taken up in approximately 300 ml. of benzene, and dried by evaporation of the benzene solution to 200 ml. Cooling of the benzene precipitated a solid contaminated with red, gummy material. Trituration of this with a little acetone left 2.86 g. (36%) of white crystals, m.p. 177–178°. After two recrystallizations from acetone, the substance melted at 178–179°.

Anal. Calc'd for $C_{14}H_{11}ClN_2O$: C, 60.2; H, 6.5.

Found: C, 60.4; H, 6.6.

(d) *Isolation of degradation products extractable from urine by butanol.* Three-liter batches of the urine remaining from the chloroform extractions were twice re-extracted with 1200-ml. portions of butanol and the extracts were evaporated under a vacuum, leaving usually from 1 to 3 g. of residue per liter of urine. This was dissolved in hot methanol, using approximately 3 ml. per g., and some of the urea and other constituents were precipitated by the slow addition of two volumes of chloroform to one of the hot methanol solution. After standing several hours, the precipitated solids were filtered off. Negligible quantities of material absorbing in the ultraviolet at 330 $m\mu$ were lost in this way. The mother liquor was evaporated under a vacuum to yield about 500 mg. of oily residue per liter of urine.

A four-plate distribution in separatory funnels (2) using 20 ml. layers of 50% aqueous methanol and chloroform served to remove some chloroform-soluble impurities which interfered with later fractionation. Tubes 0 and 1 of this distribution, in which occurred those substances more soluble in water, contained practically all of the material which absorbed light of 330 $m\mu$ wave length. These were evaporated under a vacuum and the oily residues, after material from two batches had been combined, were then distributed between 20 ml. layers of butanol and 3% ammonia. Because of the very stable emulsions formed in this system, it was necessary to centrifuge each tube for fifteen to thirty minutes after equilibration in order to separate the layers. The distribution was accordingly made in 100-ml. glass-stoppered conical centrifuge tubes rather than in the conventional separatory funnels, and the lower layers were siphoned from tube to tube. Upon completion of the distribution, which was usually carried out for 16 plates, 10 ml. of methanol was added to each tube to make the two phases mutually miscible and the concentration of quinoline was estimated with the Beckman spectrophotometer. By plotting the optical densities of each fraction at 260 and 330 $m\mu$ as ordinates against the tube numbers as abscissae it was possible to estimate the extent to which the quinoline fractions, absorbing at both wave lengths, had been separated from the constituents of normal urine which showed slight absorption at 260 $m\mu$ (Fig. 4).

Two quinoline fractions were separated by this procedure, the one occurring in tubes 0 and 1 varying from a negligible quantity to roughly 20% of the total, depending on the batch. Most of the normal constituents of urine were removed at this stage, since fractions 11 to 15 contained about 80% of the weight distributed.

The residue from the evaporation under vacuum of tubes 4 to 9 of Fig. 4 was further resolved by distribution in a 24-plate Craig apparatus between 8-ml. layers of butanol and 10% acetic acid. After completion of the distribution, the two layers in each tube were united as before by the addition of 4 ml. of methanol and the concentration measured spectrophotometrically at 260 and 330 $m\mu$ (Fig. 5).

Further purification of the main constituent in tubes 0 to 5 of Fig 5 by redistribution in the same system required the application of about 60 plates for complete separation of the quinoline from an impurity which did not absorb in the ultraviolet. Since the preceding distribution had removed from these tubes all material of partition coefficient greater than about 0.2, none of the remaining material could advance beyond the first four or five tubes in one revolution of the apparatus. It was therefore possible to apply 60 plates in the second distribution by rotating the machine two and one half times without fear of overlapping of the ends of the distribution curve.

A convenient final purification of this material was achieved by 8-plate distribution

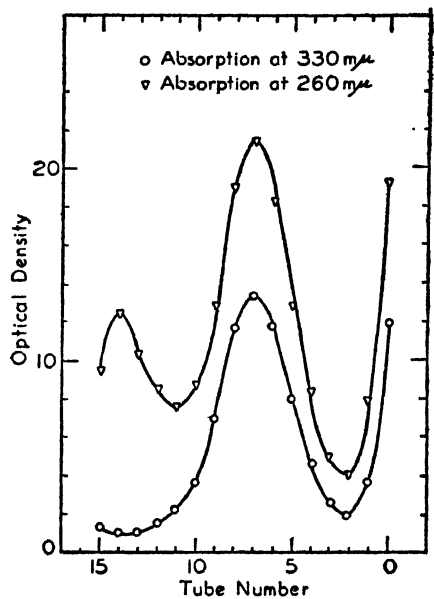


FIG. 4. DISTRIBUTION OF BUTANOL-EXTRACTABLE DEGRADATION PRODUCTS OF SN 8137 IN BUTANOL AND 3% AMMONIA

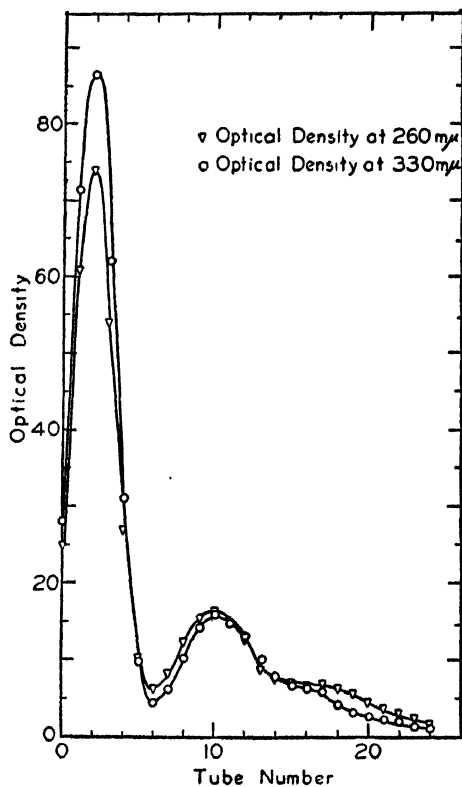


FIG. 5. DISTRIBUTION OF TUBES 4-9 OF FIGURE 4 IN. BUTANOL-10% HOAc

between 10-ml. layers of butanol and 3% ammonia, centrifuging each tube after equilibration and adding methanol as described above. Evaporation of the more concentrated fractions, 2, 3, and 4 in Fig. 6, yielded an ammonium salt as a clear brittle resin, soluble in water, slightly soluble in methanol and insoluble in non-polar solvents. Since attempted recrystallizations from water and various mixtures of water, acetone, and methanol yielded only amorphous powders, samples of the resin which had been redistributed until the experimental curves showed agreement with the theoretical distribution of a homogeneous substance were submitted for analysis. The substance contained no sulfur or phosphate. It gave a positive ninhydrin reaction. A solution of one mg. in a few drops of water after warming gently with a drop of dilute sodium hydroxide and readjustment to neutrality no

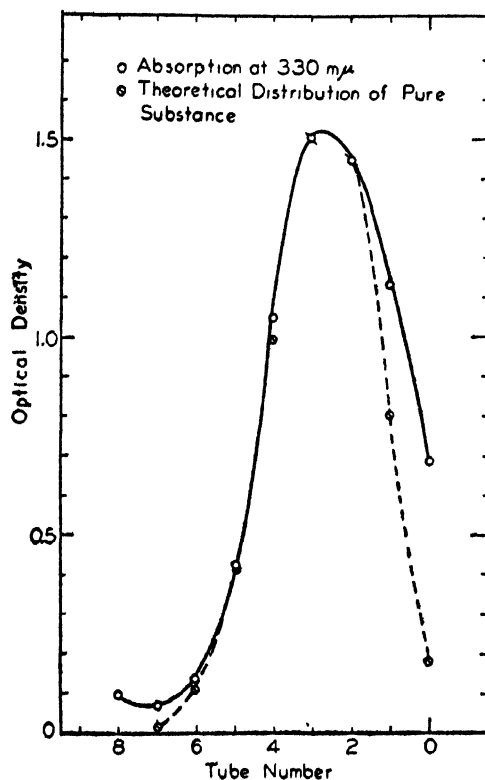


FIG. 6. DISTRIBUTION OF CONJUGATED DERIVATIVE OF SN 8137 IN BUTANOL AND 3% AMMONIA

longer gave a positive ninhydrin test. Analytical figures obtained agreed fairly well with those demanded for the N-oxide of a glycuronic acid derivative of the original drug.

Anal. Calc'd for $C_{22}H_{23}ClN_4O_8$ (the N-oxide of a glycuronide of SN-8137): C, 51.1; H, 6.4; N, 10.8; Cl, 6.9; Mol. wt. 516.8.

Calc'd for $C_{22}H_{23}ClN_4O_7$ (a glycuronide of SN-8137): C, 52.7; H, 6.6; N, 11.2; Cl, 7.1; Mol. wt. 500.8.

Found: C, 52.3; H, 6.3; N, 11.4; Cl, 6.5; Mol. wt. (from Cl analysis), 545.

The conjugation of the quinoline nucleus with a carbohydrate moiety, suggested by the analytical data, was confirmed by subjecting 10-mg. samples of the pure resin to a series of increasingly severe acid hydrolyses. After each attempt, the reaction mixture was evaporated to dryness under vacuum and the extent of hydrolysis determined by a distribution of the products between butanol and 3% ammonia.

Curve 1 of Fig. 7, in which the concentration of quinoline as determined spectrophotometrically is plotted against the tube number, illustrates the distribution of pure resin before hydrolysis; curve 2 indicates the partial liberation of the quinoline moiety by two hours refluxing in 2 *N* hydrochloric acid; and curve 3, the complete hydrolysis obtained upon heating for one hour at 130° in a sealed tube with 6 *N* hydrochloric acid. Under the latter conditions, all of the quinoline became soluble in organic solvents and was retained largely in the butanol layers upon distribution.

The presence of a uronic acid in the conjugate could be demonstrated by the naphthoresorcinol test as described by Hanson, Mills, and Williams (19) for glycuronides, except that the reagents were heated at 130° for one hour in a sealed tube before the two-hour heating at 100°.

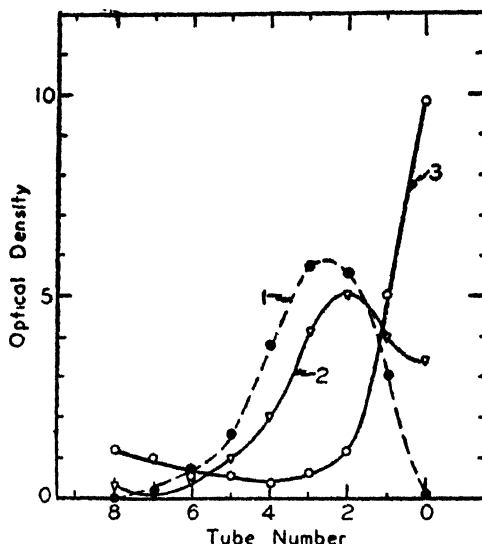


FIG. 7. Curve 1(●)—Pure SN 8137 conjugate. Curve 2(▽)—Partially hydrolyzed SN 8137 conjugate. Curve 3(O)—Completely hydrolyzed SN 8137 conjugate.

The aqueous reaction mixture from the hydrolysis of the conjugate was filtered free of charred decomposition products, made ammoniacal and extracted with chloroform. Evaporation of the extract yielded a base which accounted for one-half of the weight of the original conjugate and all of the basic material absorbing in the ultraviolet at 330 *mμ*. This material appeared to be a homogeneous substance closely related to SN-8137 when subjected to counter-current distribution. In chloroform and 2 molar phosphate buffer at pH 6.70 it exhibited partition coefficients of 0.39 and 0.49 in two separate runs. A known sample of 4-(3-diethylamino-2-hydroxypropylamino)-7-chloroquinoline when similarly distributed had a partition coefficient of 0.44. In isopropyl ether and 2-molar phosphate at pH 7.45 the constants were 1.40 for the hydrolysis product and 2.0 for the original drug (Fig. 8). Evaporation of the most concentrated, and presumably the purest, fractions from a distribution of this hydrolysis product in the latter system yielded a hygroscopic oil whose absorption curve in 95% ethanol proved identical with that of the original drug.

In spite of the excellent agreement with the theoretical distribution of a pure substance shown by the central band in Fig. 8, material isolated by evaporation of the more concentrated fractions proved to be a mixture, since treatment with two equivalents of picric acid in acetone yielded a mixture of picrates which crystallized poorly from acetone or acetone-ethanol mixtures and melted at 177–189°. The dipicrate of SN-8137 is readily crystallized from acetone and melts at 222–224°.

An attempted molecular distillation of 39 mg. of this mixture at 120° and 10^{-4} mm., under which conditions SN-8137 distills readily, yielded only 7 mg. of distillate, colored by decomposition, and some decomposition of the residue was noted.

Except for the mixed picrates of the hydrolysis product and the difficulties in distillation, the data would indicate that the original resin was the ammonium salt of the glucuronide of SN-8137, a possibility not excluded by the analytical data.

In view of the discrepancies noted in the preparation of the picrate and in the attempted distillation, the aminoquinoline portion of the conjugate would appear to have undergone some modification of the side chain. Since SN-8137 is recovered unchanged when subjected to the above hydrolytic conditions, decomposition of the drug base could not have accounted for the mixture of picrates. Although other possible alternative transformation products may be imagined, the most reasonable assumption appears to be that the conjugate is largely a glucuronide of the N-oxide of SN-8137 particularly in view of the later

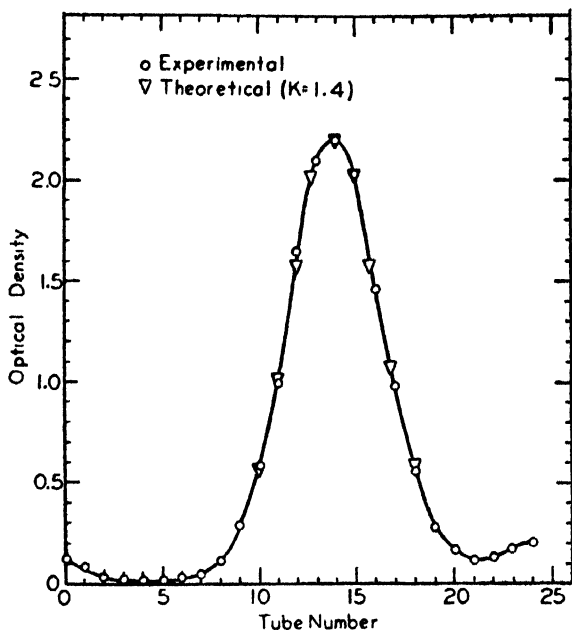


FIG. 8. DISTRIBUTION OF HYDROLYTIC PRODUCT OF SN 8137 CONJUGATE IN ISOPROPYL ETHER 2-MOLAR PHOSPHATE BUFFER ($\text{pH} = 7.45$)

experience with SN-9584. The inhomogeneous nature of the hydrolytic products may be due either to contaminants of the glucuronide or to formation of other decomposition products during the hydrolysis.

If the drug were present in the conjugate as an N-oxide, the mixture of quinoline bases isolated after hydrolysis might be expected to consist of the N-oxide together with decomposition products formed during the hydrolytic reaction. In such a case, reduction of the mixture with a mild reducing agent should make it possible to isolate the original diethylaminohydroxypropylaminochloroquinoline (SN-8137) by reduction of any amine oxide present. With this possibility in mind, a 10-mg. sample of the substance isolated from the above hydrolysis was dissolved in one ml. of 10% acetic acid and reduced by the gradual addition of 300 mg. of 2% sodium amalgam. The solution was then decanted from the mercury, the mercury washed several times with a little water, and the combined washings made ammoniacal and extracted with three 5-ml. portions of chloroform.

After evaporation of the chloroform, counter-current distribution of the product in-

chloroform and a 2-molar phosphate buffer at pH 6.58 indicated a substance 90 to 95% pure. The contents of each of the more concentrated tubes was evaporated to dryness, taken up in a few drops of acetone, and to each was added two equivalents of picric acid in a few drops of acetone. After standing several hours in the cold, a crystalline picrate melting at 186–194° was filtered off and recrystallized. About three times the volume of acetone from from which it had precipitated was required to redissolve this material. Cooling overnight deposited thin yellow needles melting at 196–198°, obtained in too small a quantity for analysis.

The combined mother liquors after partial evaporation yielded the short stubby rods characteristic of the dipicrate of SN-8137 melting at 220–223°. A mixed melting point with an authentic sample melting at 222–224° was 222–224°.

Anal. Calc'd for $C_{28}H_{28}ClN_4O_{15}$: C, 43.7; H, 3.7.

Found: C, 43.7; H, 3.7.

A second degradation product, appearing in tubes 8 to 13 of the butanol-acetic acid distribution illustrated in Fig. 5, occurred in amounts which varied with different urine samples from negligible quantities up to about one-tenth of the total butanol-extractable quinolines. Combination of all available material yielded about 30 mg. (from 12 liters of urine). An eight-plate distribution in butanol and 10% acetic acid disclosed approximately 10% of impurities when the optical density of each fraction at 330 m μ was plotted against tube number. This was eliminated by discarding the end fractions, tubes 0, 1, 7, and 8. The remaining material was combined, evaporated to dryness under vacuum, and subjected to an eight-plate distribution in butanol and 3% ammonia as previously described. Spectrophotometric analysis as before indicated the presence of about 20% of inhomogeneity in tubes 0 to 2. Evaporation of the most concentrated fractions, tubes 3, 4, and 5, yielded a solid soluble in dilute ammonia and acids, slightly soluble in hot water, and almost insoluble in methanol and organic solvents. Several recrystallizations from water were required to free the material from colored contaminants. Tubes 3 and 4 yielded white crystals melting at 163–165° in quantities too small for analysis. From tube 5 was obtained 1.5 mg. melting at 156–160°. Due to lack of material these fractions were not investigated further.

Isolation of the degradation products of 4-(3-diethylaminopropylamino)-7-chloroquinoline (SN-9584). (a) *Recovery of undegraded drug.* Three-liter batches of urine from patients receiving 400 mg. per day of SN-9584 were made ammoniacal and extracted with chloroform as previously described, yielding from 25 to 35 mg. of basic oils per liter of urine. These could be separated by a 24-plate counter-current distribution in the Craig apparatus using chloroform and 2-molar phosphate at pH 6.70, into recovered drug (tubes 0 to 8 of Fig. 9), and a smaller fraction in tubes 20 to 24 containing degradation products. Evaporation of the more concentrated fractions from the first portion of the curve yielded crystals which, after one recrystallization from ether, sintered at 72° and melted at 74–75°. The melting point 76° for an authentic sample of the drug was not depressed by mixture with this material.

Anal. Calc'd for $C_{18}H_{22}ClN_3$: C, 66.0; H, 7.6.

Found: C, 65.9; H, 7.6.

(b) *Isolation of the monoethyl compound (VI).* The fraction from tubes 21 to 24 of Fig. 9 behaved as a homogeneous substance with a partition coefficient of 1.8 upon redistribution in chloroform and 2-molar phosphate at pH 7.09. Evaporation of the more concentrated fractions from such a run, however, occasionally left a mixture of two compounds, resolvable only with difficulty by counter-current distribution in the system used, because of their identical partition coefficients, but readily separable by crystallization. In a typical run, 27 mg. of the mixture was recrystallized from acetone at 0° to yield 6.2 mg. of crystals melting at 195–200°. A second recrystallization from acetone containing a trace of methanol gave 4.5 mg. of leaflets melting at 201–203°.

Anal. Calc'd for $C_{14}H_{20}ClN_2O_2$: C, 56.5; H, 6.7; N, 14.1.

Found: C, 56.4; H, 6.2; N, 14.0.

From 2.4 mg. of this substance was obtained 4 mg. of a picrate which crystallized from acetone at room temperature as rosettes of short compact needles, m.p. 232–236°.

Anal. Calc'd for $C_{20}H_{23}ClN_6O_9$: C, 45.6; H, 4.4.

Found: C, 45.4; H, 4.3.

The absorption spectrum in chloroform of this substance was not changed from that of the original drug, making it somewhat unlikely that there was any modification of the original 4-amino-7-chloroquinoline nucleus. The analytical data would suggest then that the extra oxygen to be accounted for had in some way entered the side chain of the major degradation product, possibly to form a hydrated hydroxylamine derivative. This compound was isolated in quantities sufficient only to secure the analytical data. In certain later batches of urine only the monoethylaminopropylamino-7-chloroquinoline (VI) appeared in the second fraction, while in others a small amount of the above compound was present.

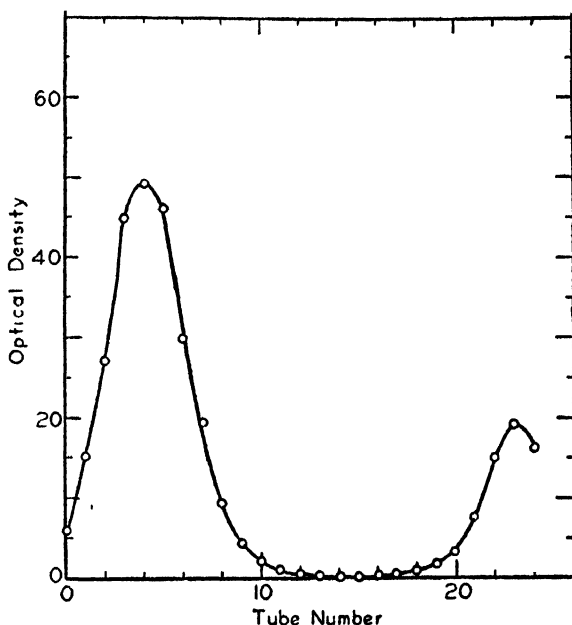


FIG. 9. DISTRIBUTION OF $CHCl_3$ -EXTRACTABLE DEGRADATION PRODUCTS OF SN 9584 IN CHC AND 2-MOLAR PHOSPHATE ($pH = 6.70$)

The mother liquors from the crystallization of the unknown derivative described above were evaporated to dryness and the residue was redistributed in butanol and a 2-molar phosphate buffer at pH 6.8, in which system the material behaved as a homogeneous substance with a partition coefficient of 1.27. An authentic sample of 4-(3-ethylaminopropylamino)-7-chloroquinoline (SN-13,588), showed a constant of 1.20 when distributed in the same system.

The fractions near the maximum of the distribution curve (Fig. 9) were evaporated taken up in a little chloroform and freed from traces of butanol and buffer by several washings with water. Evaporation of the chloroform solution left a hygroscopic crystalline solid melting at 65–79°. Recrystallization of a sample weighing 13.7 mg. from dilute acetone at 0° yielded 8.3 mg. of plates, m.p. 65–75°. A sample of the synthetic product treated identically melted at 65–78°. Distillation of these substances at 100° and 10^{-3} mm. did not change the melting point, which was not depressed upon mixing the two samples.

The dipicrate of the degradation product crystallized from acetone in small rosettes, m.p. 251–253°.

Anal. Calc'd for $C_{28}H_{34}ClN_2O_{14}$: C, 43.3; H, 3.3.

Found: C, 43.6; H, 3.1.

A dipicrate of authentic SN-13,588 melted at 251–253°. The melting point was not depressed on mixing with the picrate of the degradation product.

(c) *Isolation of degradation products extractable from urine by butanol.* Urines which had been extracted with chloroform were further extracted with butanol as described previously for the isolation of the excreted derivatives of SN-8137. The same procedure of precipitation with methanol and chloroform and distribution between chloroform and 50% methanol was followed. Fractions 0 and 1 of the chloroform-methanol distribution were

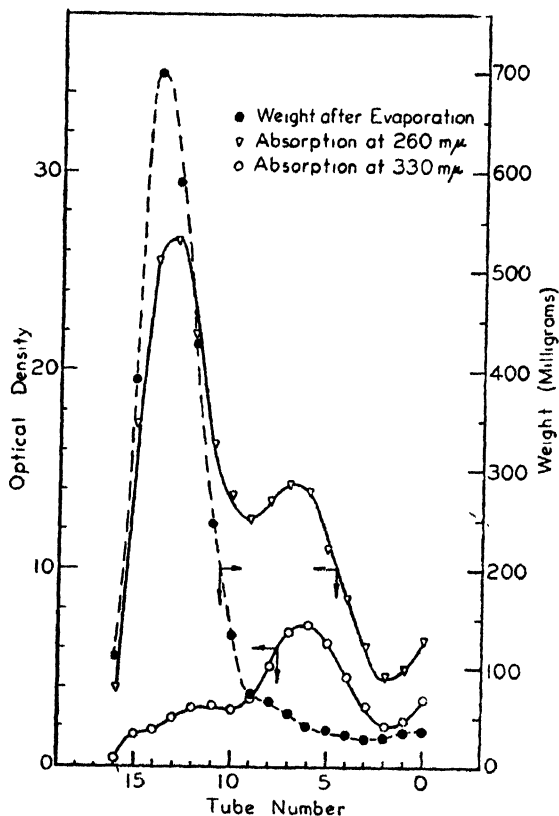


FIG. 10 DISTRIBUTION OF BUTANOL-EXTRACTABLE FRACTION FROM SN 9584 IN BUTANOL AND 3% AMMONIA

combined, evaporated, and the residue distributed in butanol and 3% ammonia exactly as before, centrifugation again being required after each equilibration to overcome the heavy emulsification. Eighty-six per cent of the total weight of the mixture was concentrated into tubes 10 to 16 of this distribution (Fig. 10), permitting the isolation in tubes 2 to 9 of a quantity of quinoline compounds corresponding to about 12 mg. per liter of urine.

This fraction was further resolved into three components upon evaporation and redistribution in a Craig apparatus with butanol and 10% acetic acid. As before, methanol was added to each tube of the machine upon the completion of 24 equilibrations and the optical densities of the resulting homogeneous solutions measured at both 260 and 330 mμ (Fig. 11). The decided difference in intensity of absorption noted at 260 and 330 mμ indicated considerable contamination of the fractions occurring in maximum concentration in tubes 12 and 19 with constituents of normal urine, since the intensity of absorption at these two wave

lengths approached the same value in the butanol, methanol, acetic acid solution as the material approached homogeneity.

Some improvement in the separation of the fractions from each other and from contaminants could be achieved by the application of a greater number of plates, using the withdrawal technique as described by Craig (1). A total of thirty-nine plates was applied to the mixed degradation products of SN-9584, as illustrated in Fig. 12. Because of the series of withdrawals, this curve is not continuous, the portion to the right of the discontinuity representing the fractions withdrawn. Tube 39 represents the first fraction withdrawn and would correspond to the twenty-fourth tube of a twenty-four-plate distribution. Tube 38 corresponds to the twenty-fourth plate of a twenty-five-plate distribution, etc. The fractions to the left of the discontinuity, which were those remaining in the machine at the

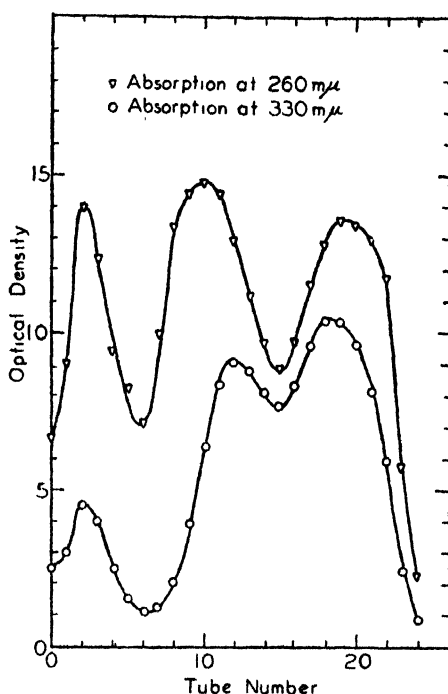


FIG. 11. CONTENTS OF TUBES 2-9 OF FIGURE 10 DISTRIBUTED IN BUTANOL AND 10% ACETIC ACID

time of the last withdrawal, have all been subjected to the full thirty-nine equilibrations.

(d) *Isolation of N-(7-chloroquinolyl-4)-β-alanine*. The combined contents of tubes 10 to 23 of the 39-plate (Fig. 12) distribution were evaporated and freed of most remaining contaminants by 16-plate distribution in 10-ml. layers of butanol and 3% ammonia in centrifuge tubes as previously described. The purest material from tubes 6 to 8, amounting to approximately 18 mg., was freed of impurities, which did not absorb in the ultra-violet, by several recrystallizations from hot water to yield about 6 mg. of colorless crystals which melted and resolidified from 130–145° and finally melted at 267–269°. A synthetic sample of N-(7-chloroquinolyl-4)-β-alanine behaved identically and the melting point was not depressed on mixture of the samples.

Anal. Calc'd for $C_{12}H_{11}ClN_2O_2$: C, 57.5; H, 4.5.

Found: C, 57.1; H, 4.5.

Synthesis of N-(7-chloroquinolyl-4)-β-alanine: (Columbia). A solution of 10 g. of 4,7-dichloroquinoline and 9 g. of β-alanine in 40 g. of phenol was heated with vigorous stirring

for one hour at 160°. When the brown reaction mixture had cooled, it was shaken with 150 ml. of 10% potassium carbonate solution and 250 ml. of ether. The ether layer was decanted from the heavy emulsion which settled in the lower layer. A second extraction with 200 ml. of ether gave a clean separation of the clear layers. After a third ether extraction, the combined extracts were back extracted with several 100-ml. portions of 10% potassium carbonate solution.

The combined aqueous solutions, which showed a blue fluorescence, were neutralized to pH 7 with 65 ml. of 6 *N* hydrochloric acid. The finely divided precipitate which formed slowly on standing overnight in the refrigerator was filtered off yielding 8.5 g. (63%) of material which melted, after preliminary melting and resolidification between 130° and 145°, at 265–268°. This material could be recrystallized from boiling water, using about 200 ml. per g., with a recovery of 85%. A 1-g. sample recrystallized twice yielded 729 mg. which first began to melt on the hot stage at 130°, had completely resolidified at 145°, and finally melted at 267–269°.

Anal. Calc'd for $C_{12}H_{11}ClN_2O_2$: C, 57.5; H, 4.5.

Found: C, 57.1; H, 4.5.

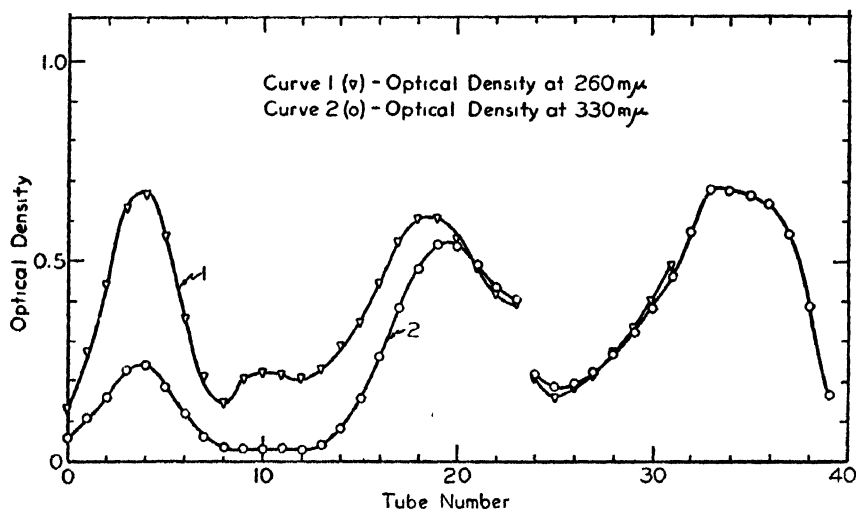


FIG. 12. DISTRIBUTION OF BUTANOL-EXTRACTABLE DEGRADATION PRODUCTS OF SN 9584 IN BUTANOL AND 10% ACETIC ACID

Another sample of the first precipitate obtained above was distributed in an 8-plate run with butanol and 10% acetic acid, using 10-ml. layers in separatory funnels. After the last equilibration, 5 ml. of methanol was added to each tube, and the concentration was estimated spectrophotometrically. The contents of the most concentrated fraction, tube 4, was evaporated under vacuum and the dry residue analyzed.

Anal. Found: C, 57.2; H, 4.6.

Preparation of the methyl ester with diazomethane apparently resulted in the simultaneous methylation of the nitrogen at the 4 position. To 6 ml. of 40% potassium hydroxide solution and 15 ml. of ether at 0° was added 1 g. of *N*-nitrosomethyl urea. The yellow ether layer was decanted and to it was added about 500 mg. of *N*-(7-chloroquinolyl-4)- β -alanine.

The finely divided solid was washed into the ether with approximately 10 ml. of methanol and the solution was allowed to stand overnight in the refrigerator during which time most of the suspended solid dissolved. Evaporation of the solvent left an oil which crystallized to a yellow-white solid after standing several hours. This was taken up in hot 95% ethanol. Cooling precipitated colorless rectangles melting at 148–149°. After two recrystallizations from ethanol, the material still melted at 148–149°.

Anal. Calc'd for $C_{14}H_{13}ClN_2O_2$: C, 60.3; H, 5.3.

Found: C, 59.8; H, 5.3.

Preparation of N-(7-chloroquinolyl-4)glycine (Columbia). A mixture of 10 g. of 4,7-dichloroquinoline, 8.25 g. of glycine and 30 g. of phenol in a 500-ml. flask equipped with stirrer, thermometer, and air-cooled reflux condenser was heated for one hour at an internal temperature of 165–170° with stirring. After cooling, the reaction mixture was shaken between 200 ml. of ether and 200 ml. of 10% sodium carbonate solution and each layer was back extracted with 200 ml. of the other solvent. The aqueous solution was warmed with 5 g. of decolorizing carbon (Norit), filtered and neutralized with 110 ml. of 1 *N* sodium hydroxide solution to pH 6.5. On standing overnight in the cold, 7.8 g. of finely divided white precipitate separated, melting at 253–255° with decomposition. The material when tested for homogeneity by counter-current distribution in butanol and 10% acetic acid behaved as a homogeneous substance, but contained about 1% of ash, from which it was liberated by recrystallization from water.

Anal. Calc'd for $C_{11}H_9N_2O_2$: C, 55.82; H, 3.8.

Found: C, 55.5; H, 3.6

The product was methylated with diazomethane as before yielding a dimethyl compound which melted at 214.5–215° after two recrystallizations from ethanol.

Anal. Calc'd for $C_{13}H_{13}ClN_2O_2$: C, 59.9; H, 5.01.

Found: C, 59.4; H, 5.2.

The two fractions in tubes 0 to 5 and 18 to 24 of Fig. 12 remain to be investigated. That they are degradation products of SN-9584 is indicated by the fact that normal urine when carried through an identical fractionation procedure gave no fraction corresponding to them.

Material isolated from tubes 0 to 4 of Fig. 12 was redistributed in butanol and 10% acetic acid, but only oils were obtained upon evaporation of the most concentrated fractions. No chloroform extractable quinoline bases were liberated from this material when it was subjected to acid hydrolysis under conditions comparable to those used with the conjugate of SN-8137.

SUMMARY

Attempts to isolate degradation products from the urine of men receiving representative antimalarials of the 4-aminoquinoline (chloroquine) type have revealed a series of transformation products. The quinoline nucleus is apparently not involved in these transformations. An ethyl group attached to the terminal nitrogen of the side chain is first removed probably by oxidation. Apparently oxidation of the terminal nitrogen to an oxide type of compound then results and finally complete removal of the terminal basic group results with the formation of an acid.

Another type of transformation involves the formation of a conjugate of the uronic acid type. In this type of transformation oxidation of the terminal nitrogen also appears to be involved.

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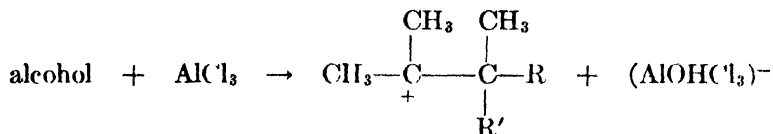
FRAGMENTATION OF 2,3,4-TRIMETHYL-2-PENTANOL WHEN CONDENSED WITH BENZENE IN THE PRESENCE OF ALUMINUM CHLORIDE

RALPH C. HUSTON AND REINHOLD J. KRANTZ

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In a previous paper (1) from this laboratory, it was observed that attempts to condense 2,3,4-trimethyl-2-pentanol with benzene in the presence of aluminum chloride at a temperature of -15° resulted in a mixture of hydrocarbons which distilled over a wide range below the boiling points of the octylbenzenes. There was no isolation of 2,3,4-trimethyl-2-phenylpentane.

In other fragmentation studies (2, 3, 4) of various tertiary alcohols, large yields of tertiary butylbenzene have been obtained. It is presumed that the fragmentation results from the carbonium ion, which was present in each of the above cases, either directly by the removal of the hydroxyl ion, or indirectly by rearrangement.



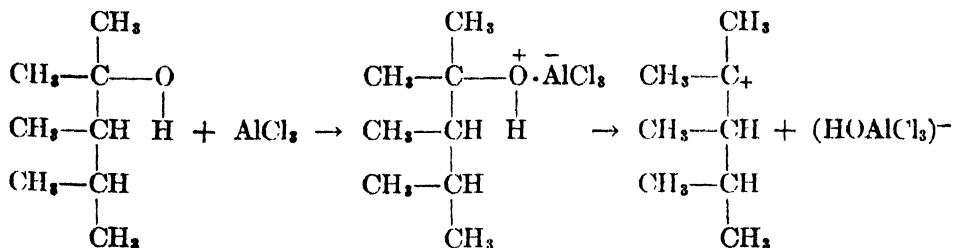
R' = methyl or H.

R = methyl, ethyl, or isopropyl.

Condensation of 2,3,4-trimethyl-2-pentanol with benzene, activated by aluminum chloride, gave the following products: 2-methylpropane (7%); 2,3,4-trimethyl-2-chloropentane (23%); 2-methyl-2-phenylpropane (28%); olefin, $\text{C}_{11}\text{H}_{22}$ (2%); 2-methyl-2-phenylbutane (3%); olefin, $\text{C}_{12}\text{H}_{24}$ (5.5%); 2,3,4-trimethyl-2-phenylpentane (6%); plus other alkyl chlorides.

To facilitate separation of the fractions, the products were treated with 50% alcoholic potash to give olefins in place of the alkyl chlorides.

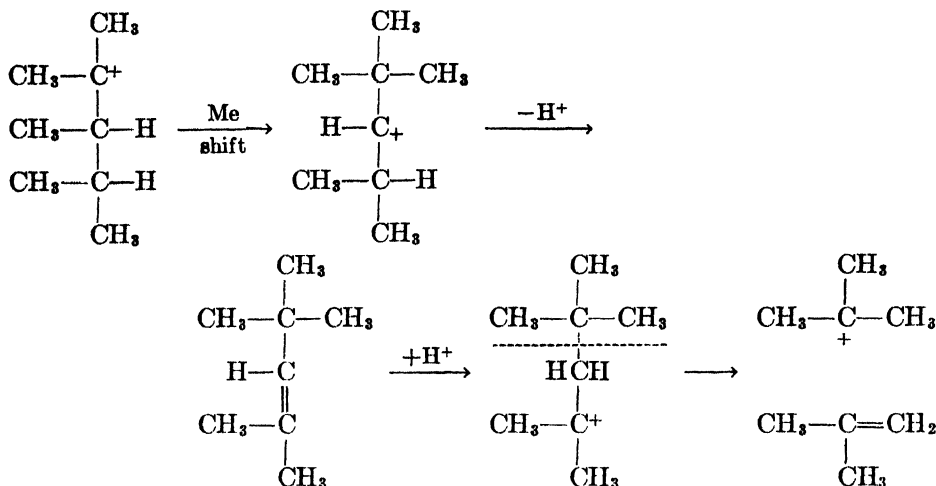
It is assumed, as in other reactions of alcohol and aluminum chloride (2, 3), that the initial step is the formation of the dative bond between the nucleophilic catalyst and the carbinol, followed by the formation of the octyl cation.



Normally one would expect the octyl carbonium ion to react with the activated benzene nucleus, but due to the instability of the cation only 6% of the octylbenzene is obtained.

The octyl cation can rearrange, undergo chain rupture, lose a proton to form an olefin, add a chloride ion, add to a fragment to give a higher olefin, or react directly with the activated benzene nucleus. All of these possible reactions occur.

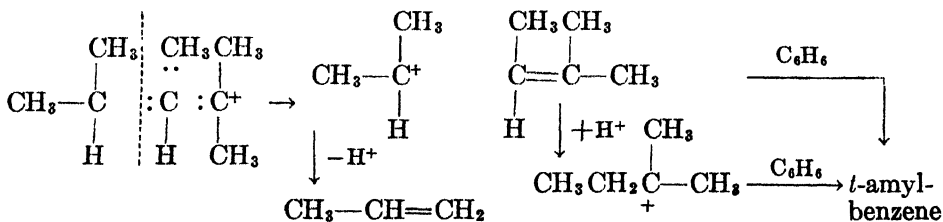
The low yield of the expected product and high yield of the *t*-butylbenzene is attributed to the tendency of the cation to undergo rearrangement (5) with resulting rupture of the chain.



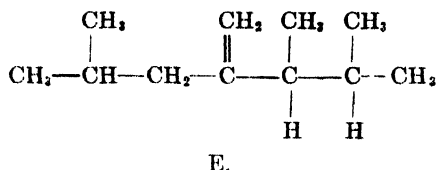
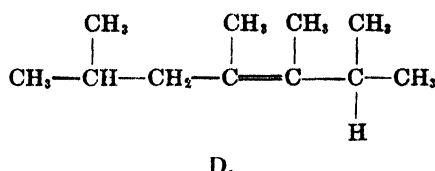
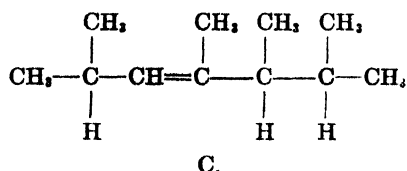
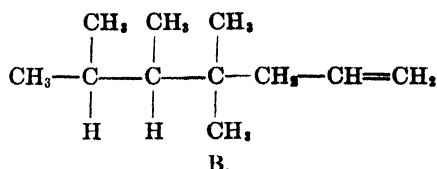
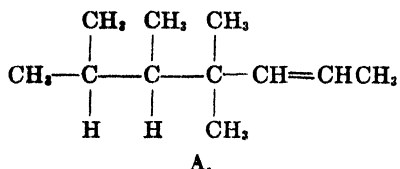
Either one of the fragments resulting from the chain rupture is capable of condensing with benzene to give 2-methyl-2-phenylpropane, or the olefin might add a proton before the condensation.

The mechanism of the formation of isobutane is difficult to explain. Although there are numerous references in the literature to such reductions in the presence of aluminum chloride, none has offered a simple explanation. In the isomerization of alkanes in the presence of aluminum chloride, Komarewsky (6) always found large quantities of isobutane as well as olefins of greater carbon content.

The electron density in the octyl cation is such that chain rupture can occur without rearrangement. The electrons are drawn in the direction of the positive carbon, creating the tendency to release a cation from the adjacent carbon. It is significant that the isopropyl group is released more readily than the methyl group. Huston and Barrett (3) have shown that condensation of 2,3,3-trimethyl-2-butanol with benzene gave considerable chloromethane. Since none was obtained, it appears that the electron pair is closer to the methyl group than to the isopropyl group.



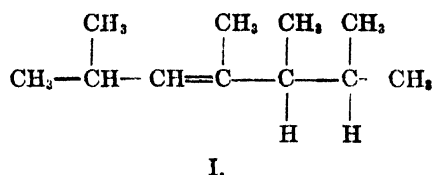
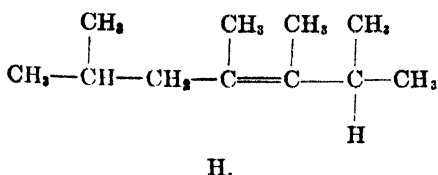
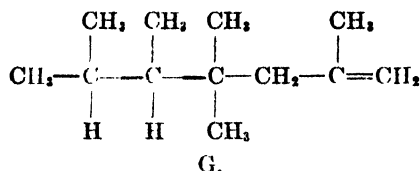
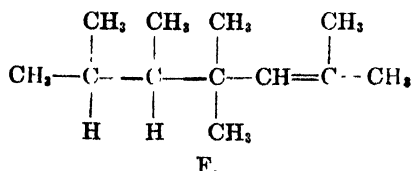
It is believed that the octyl cation adds to propene to give two isomeric eleven-carbon olefins (A and B) after loss of a proton. Although less likely according to polymerization studies, three other possible olefins (C, D, and E) could form by the addition of the isopropyl cation to 2,3,4-trimethyl-1-pentene.

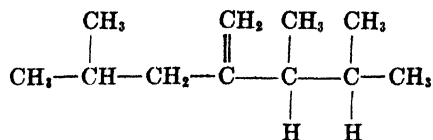


In the dehydration of an analogous alcohol, 4,4-dimethyl-2-pentanol, Whitmore (7) has shown that the ratio of 4,4-dimethyl-2-pentene to 4,4-dimethyl-1-pentene is 4.5 to 1. This would indicate a preponderance of A over B.

In a similar manner the octyl cation can add to isobutene to give two isomeric twelve-carbon olefins. Theoretically possible, also, are three other olefins (H, I, and J) formed by the addition of the tertiary butyl cation to 2,3,4-trimethyl-1-pentene. Although all five of the olefins may be present, the formation of F and G seems most plausible.

In the dehydration of 2,4,4-trimethyl-2-pentanol, Whitmore (8) has shown that the ratio of 2,4,4-trimethyl-1-pentene to 2,4,4-trimethyl-2-pentene is four-to-one. By analogy, one would expect a greater amount of G in this fraction.





J.

When the twelve-carbon olefins were hydroxylated and oxidized with perchloric acid, acetone was found present in small amounts. This should indicate the presence of F.

The proof of the structure of 2,3,4-trimethyl-2-phenylpentane was made by nitration, reduction of the amine, and diazotization to 2,3,4-trimethyl-2-*p*-hydroxyphenylpentane. The phenol thus obtained was identical with the product of the condensation of the carbinol with phenol. This was ascertained by the mixed melting points of their α -naphthylurethan derivatives.

In the condensation of 2,3,4-trimethyl-2-pentanol with phenol, less fragmentation took place and the chief product was the *p*-octylphenol with lesser amounts of *p*-*t*-butylphenol and a trace of 2-methylpropane. There was also evidence of the presence of some 2,4,4-trimethyl-2-*p*-hydroxyphenylpentane.

EXPERIMENTAL

Preparation of 2,3,4-trimethyl-2-pentanol. The alcohol was prepared by the reaction of methyl Grignard and ethyl 2,3-dimethylbutanoate. The ester was prepared by a series of reactions developed by Huston and Goerner (9). They include a Reformatsky reaction of acetone and ethyl 2-bromopropionate to give ethyl 3-hydroxy-2,3-dimethylbutanoate; this was followed by dehydration with phosphorus pentoxide to give two isomeric unsaturated esters, and subsequent hydrogenation of these unsaturated esters with platinum catalyst gave ethyl 2,3-dimethylbutanoate.

The total yield of carbinol based on the bromo ester was 35–40%; b.p. 49.5°/7 mm; n_D^{20} 1.4350; d_4^{20} 0.8432.

Condensation of 2,3,4-trimethyl-2-pentanol. A 1-liter 3-necked flask was equipped with dropping-funnel, stirrer, and condenser which contained a delivery tube through a Dry Ice-acetone trap. In a typical run, 130 g. (1 mole) of carbinol was added dropwise with vigorous stirring to a suspension of 44.5 g. ($\frac{1}{3}$ mole) of aluminum chloride in 450 ml. (5 moles) of anhydrous, thiophene-free benzene. The temperature was kept at $34 \pm 1^\circ$. After the addition of the carbinol (2.5 hours), the mixture was stirred for an additional hour, allowed to stand all night, and hydrolyzed with 125 ml. of ice-water.

The benzene layer was separated, washed with water and with sodium carbonate. After drying over sodium sulfate the benzene was removed at atmospheric pressure and the condensation products fractionated. The gas collected in the Dry Ice trap was combined with the gas given off when the benzene was removed.

Identification of 2-methylpropane. The gas collected in the Dry Ice-acetone trap was fractionally distilled until free from hydrogen chloride and benzene. An Anschütz thermometer then measured the boiling point at -11° to -10° . Since refractive index readings are often better indications of purity than boiling points, an adaptation of a method by Grosse (10) for determining refractive indices at low temperatures was used.

The two lenses of the refractometer were protected from frosting over with the moisture of the room by covering them with a glass plate sealed on the sides with vaseline. A thermometer was calibrated at -25° , and acetone with some solid carbon dioxide was passed back and forth through the system. After becoming familiar with the apparatus, a temper-

TABLE I
(3-MOLE BASIS)
FRACTIONATION OF PRODUCTS

FRACTION IDENTIFIED	B.P., °C. (738 MM.)	n_D^{20}		DERIVATIVE OR MEANS OF IDENTIFICATION	YIELD, GRAMS
		Obs.	Lit.		
2-Methylpropane	-11 to -10	1.3515 (-25°)	1.3514 (10)	Phys. Const.	25
2,4,4-Trimethyl-1-pentene	101-102	1.4099	1.4089 (11)	Phys. Const.	4
2,3,4-Trimethyl-1-pentene	107-108	1.4145	1.4146 (12)	Phys. Const.	45
2,3,4-Trimethyl-2-pentene	114-115	1.4230	1.423 (11)	Phys. Const.	55
2-Methyl-2-phenylpropane	168.5	1.4918	1.4918	<i>p</i> -acetamino deriv., m.p. 168°	115
C ₁₁ H ₂₂	177-180	1.4490		Calc'd: C, 85.71; H, 14.29; M.W., 154 Fd: C, 85.62; H, 14.13; M.W., 153.5	8
2-Methyl-2-phenylbutane	189	1.4928		<i>p</i> -acetamino deriv., m.p. 138-39°	13
C ₁₂ H ₂₄	189-197	1.4620		Calc'd: C, 85.71; H, 14.29; M.W., 168 Fd C, 85.89; H, 14.05; M.W., 171	25
2,3,4-Trimethyl-2-phenylpentane*	235	1.4958		Calc'd: C, 88.33; H, 11.67; M.W., 190 Fd C, 88.27; H, 11.50; M.W., 193 α -naphthylurethan of <i>p</i> -hydroxy deriv. m.p. 139°	35

*Four grams of distillate came over between 230° and 233°. This had an index of refraction of 1.4935 which is near that of 2,4,4-trimethyl-2-phenylpentane. It was not pure enough to give sharp melting derivatives.

ature of $-25^\circ \pm 1^\circ$ could be maintained. Three possible gases possess the following physical properties:

Compound	B. P., °C.	n_D^{20}
<i>n</i> -butane.	-0.5	1.3621
isobutane	-10.2	1.3514
isobutylene	-6.0	1.3814

The observed refractive indices varied from 1.3512 to 1.3518 in about ten readings, using different samples from different condensations.

Fractionation of the condensation product. This was accomplished at reduced pressure in a 24-inch Fenske type column, packed with $\frac{1}{8}$ inch glass helices. To facilitate separation, the condensate was refluxed three to four hours with an equal volume of 50% alcoholic potassium hydroxide. The resulting emulsion was washed with water, dried over sodium sulfate, and fractionated. The fractions are shown in table I.

Identification of 2,3,4-trimethyl-2-phenylpentane. One-half mole of aluminum chloride was mixed with 200 ml. of Skellysolve in the apparatus described under the condensation of the carbinol. The phenol (1.2 moles) was dissolved in 1 mole of carbinol and the solution added slowly through the dropping-funnel, with the temperature of the reaction flask maintained at 25–30°. After all of the solution had been added, the mixture was allowed to stand all night and hydrolyzed the next morning with ice-water. The organic layer was dried and the solvent removed at atmospheric pressure. At this time 1 g. of 2-methylpropane, which had been dissolved in the Skellysolve, was collected in a Dry Ice-acetone trap.

Careful fractionation gave the two olefins resulting from the dehydration of the carbinol, 2,3,4-trimethyl-2-chloropentane, and unreacted phenol.

The residual mass was transferred to a small flask and distilled through a 12-inch Vigreux column. Two main fractions were obtained.

I. 110–125°/5 mm.	10 g.
II. 130–140°/5 mm	23 g.

Repeated crystallizations after redistillation of I yielded a solid phenol, m.p. 95–96°. The benzoyl ester of this phenol melted at 80–81°. Mixed melting point with the benzoate of *t*-butylphenol showed no depression.

Fraction II had the m.p. 80–83°. Fractional crystallization resulted in a phenol, melting at 88–89°. Its α -naphthylurethan melted at 138–139°, and its benzoate at 113–115°. The initial melting range of fraction II indicates the presence of some 2, 4, 4-trimethyl-2-hydroxyphenylpentane with 2, 3, 4-trimethyl-2-*p*-hydroxyphenylpentane (13).

Nitration, reduction, and diazotization of 2,3,4-trimethyl-2-phenylpentane gave a phenol whose α -naphthylurethan or benzoate showed no melting point depression when mixed with those obtained directly from condensation of the alcohol with phenol.

EAST LANSING, MICH.

SUMMARY

1. 2,3,4-Trimethyl-2-pentanol was condensed with benzene in the presence of aluminum chloride. Only 6% of the expected 2,3,4-trimethyl-2-phenylpentane was obtained.

2. Proof of the structure of 2,3,4-trimethyl-2-phenylpentane was obtained by nitration of the octylbenzene, reduction, and diazotization to give an octylphenol identical with one obtained by direct condensation of the carbinol with phenol.

3. The gas, 2-methylpropane, was identified by its b.p., and refractive index at –25°.

4. Chain rupture, both before and after rearrangement, gave a small amount of *t*-amylbenzene, and a 28% yield of *t*-butylbenzene. Possible mechanisms are suggested.

5. Mixed eleven- and twelve-carbon olefins were found.

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AN OBSERVATION ON THE RELATION BETWEEN THE MELTING POINTS OF THE DISUBSTITUTED ISOMERS OF BENZENE AND THEIR CHEMICAL CONSTITUTION

ALBERT C. HOLLER

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In an investigation of the melting points of the disubstituted derivatives of benzene, it was noticed that a definite relationship does exist between the melting point of the isomers and their chemical constitution.

The derivatives were placed in one of two classes on the basis of their structure. Class A, in which the disubstituted derivative contains *one* ortho-para orienting group (1, 2, 6); and *one* meta orienting group (1, 2, 6); and Class B, in which the disubstituted derivative contains *two* ortho-para orienting or *two* meta orienting groups.

Division of Groups. The substituent groups were divided into two classes, those that are meta orienting and those that are ortho-para orienting in character. Table I lists the various groups according to these properties.

The Order of the Melting Points for the Disubstituted Derivatives of Benzene. The following rules are postulated from the data collected on the melting points of the disubstituted derivatives of benzene:

Rule I. When the disubstituted benzene derivative contains *one* meta orienting group and *one* ortho-para orienting group, the order of the melting points for the isomers is: ortho < meta < para.

Rule II. When the disubstituted benzene derivative contains *only* ortho-para orienting or *only* meta orienting groups, the order of the melting points for the isomers is: meta < ortho < para.

In Table II are listed the melting points of various disubstituted derivatives of benzene containing *one* ortho-para orienting group and *one* meta orienting group. It is seen by inspection that Rule I holds.

In Table III are recorded the melting points of the various disubstituted derivatives of benzene containing *only* ortho-para orienting groups or *only* meta orienting groups. The order of the melting points for these isomers follows Rule II, namely $m < o < p$.

DISCUSSION

At the present time no satisfactory explanation to account for Rules I and II is evident.

In view of the complex interplay of factors affecting the absolute values of melting points, it was anticipated that some exceptions to the postulated rules would exist.

It is well known that the melting points of organic compounds are not readily predicted. This paper allows one to predict with reasonable accuracy the order of the melting points of the isomers of the disubstituted derivatives of benzene and should be of value in both applied and theoretical organic chemistry.

TABLE I
DIVISION OF GROUPS

META ORIENTING GROUPS	ORTHO-PARA ORIENTING GROUPS
$-\text{NO}_2$ $-\text{C}\equiv\text{N}$ O \parallel $-\text{C}-\text{CH}_3$ O \parallel $-\text{C}-\text{H}$ O \parallel $-\text{C}-\text{OH}$ $-\text{N}=\text{O}$ OCH_3 \diagup $-\text{C}$ \parallel O NH_2 \diagup $-\text{C}$ \parallel O $-\text{SO}_3\text{H}$ O \parallel $-\text{C}-\text{Cl}$	$-\text{N}(\text{CH}_3)_2$ $-\text{N}(\text{COCH}_3)_2$ $-\text{NH}_2$ $-\text{OH}$ $-\text{O}-\text{CH}_3$ $-\text{O}-\text{C}_2\text{H}_5$ $-\text{F}$ $-\text{Cl}$ $-\text{Br}$ $-\text{I}$ $-\text{CH}_3$ $-\text{C}_2\text{H}_5$ $-\text{NHCOCH}_3$ O \parallel $-\text{O}-\text{C}-\text{CH}_3$ $-\text{C}_6\text{H}_5$ $-\text{CH}_2\text{COOH}$ $-\text{CH}=\text{CHCOOH}$ $-\text{N}=\text{NC}_6\text{H}_5$ $-\text{CH}_2\text{CN}$ $-\text{CH}_2\text{Cl}$ $-\text{CH}_2\text{Br}$ $-\text{CHCl}_2$

ACKNOWLEDGMENT

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TABLE II
MELTING POINTS FOR RULE I DISUBSTITUTED DERIVATIVES OF BENZENE

DISUBSTITUTED DERIVATIVE	MELTING POINT OF ISOMER, °C (3, 4, 5)		
	Ortho	Meta	Para
(a) Amino derivatives			
aminobenzamide	108	113-114	182.9
aminobenzoic acid	144-145	173-174	187-188
aminobenzonitrile	51	53	86
(b) Hydroxy derivatives			
hydroxybenzaldehyde	-7	106	116-117
hydroxybenzoic acid	159	201	214.5
(c) Halogen derivatives			
chlorobenzaldehyde	11	17-18	47.8
iodobenzaldehyde	37	57	77
fluorobenzamide	116	130	154.5
iodobenzamide	183.6	186.5	217.6
fluorobenzoic acid	120-122	124	182-184
chlorobenzoic acid	141-142	158	242-243
bromobenzoic acid	148	154	251
iodobenzoic acid	-28.5	162	187.5
fluoronitrobenzene	-5.9	1.7	26.5
chloronitrobenzene	32.5	44.4	83.5
bromonitrobenzene	43	56	127
(d) Methoxy and ethoxy derivatives			
ethoxybenzoic acid	19-20	135-137	195
methoxybenzoic acid	98	107-108	184.2
(e) Nitro derivatives			
nitroacetanilide	93	155	215
nitroaniline	71.5	114	146-147
nitroanisole	9.4	38	54
nitrobenzyl bromide	46-47	58	100
nitrophenatole	5-6	34	59-60
nitrodiphenyl	37	61	113-114
nitrophenol	44-45	96-7	113-114
nitrotoluene	α , -10.6 β , -4.1	15.5	51.3
(f) Toluene derivatives			
toluic acid	104-105	110-111	179-180
(g) Miscellaneous derivatives			
acetamidobenzoic acid	184-186	249	252
phenylbenzoic acid	113-114	160-161	219-220
(h) Exceptions			
bromobenzamide	156	150	190
bromobenzonitrile	51	38	113
chlorobenzamide	141	134.5	178.3
ethylbenzoic acid	67	47	112-113
hydroxyacetanilide	203	149	168
hydroxybenzamide	140	170.5	162
iodo-nitrobenzene	49.4	36	171.5
toluamide	147	97	165
tolunitrile	-13	-23	29.5
nitrobenzyl chloride	48-49	45-47	71
nitrobenzyl cyanide	84	61-62	116-117
nitrocinnamic acid	243-245	200-201	286-288
nitrosotoluene	72.5	53.5	48.5

TABLE III
MELTING POINTS FOR RULE II DISUBSTITUTED DERIVATIVES OF BENZENE

DISUBSTITUTED DERIVATIVE	MELTING POINT OF ISOMER, °C (3, 4, 5)		
	Meta	Ortho	Para
(a) Two meta orienting groups			
sulfobenzoic acid.	98	105	260
dinitrobenzene.	89.8	117	173
nitrobenzamide.	142-143	176.6	200-201
nitrobenzoic acid.	140-141	147.5	240-242
(b) Two ortho-para orienting groups			
aminodiphenyl	30	45-46	50-52
aminophenol.	122	173	184-186
anisidine.	< -12	5.2	59
aminoacetanilide	70	132	161-162
acetylanisidine	80	87-88	137-138
acetotoluide	65.5	110	153
bromoacetanilide	87.5	99	168
aminoazobenzene	57	123	126
chloroacetanilide	72.5	88	178.4
diaminobenzene	62.8	103	140
diethoxybenzene	12.4	43-45	71-72
dimethylbenzene	-47.4	-25	13.2
dimethoxybenzene	-52	22.5	56
ethylaniline	-64	-43	-5
hydroxyphenylacetic acid	129	145-147	148
methoxyphenol	< -17.5	28.3	53
methylacetanilide	65.5	110.4	146-147
xylylene cyanide.	28-29	59-60	98
toluidine	-31.5	α , -24.4 β , -16.3	43.7
xylenedibromide	77	94.5	144
xylenedichloride	34.2	55	100.5
(c) Dihalo benzenes			
dibromobenzene	-6.9	1.8	87.8
dichlorobenzene	-24.8	-17.6	53
(d) Halo anilines			
fluoroaniline	—	-34.6	-1.9
chloroaniline	-10.4	0.0	71
bromoaniline.	18.5	31.5	66.4
iodoaniline.	27	56.5	62
(e) Halo phenols			
fluorophenol	13.8	16.1	28.5
iodophenol	40	40.4	94
(f) Halo toluenes			
fluorotoluene.	-110.8	< -80	—
chlorotoluene.	-47.8	-34	7.5
bromotoluene.	-39.8	-28	28.5
(g) Miscellaneous derivatives			
chlorobromobenzene.	-21.2	-12.6	67.4
bromoiodobenzene.	-9.3	-2.1	92

TABLE III—*Concluded*

DISUBSTITUTED DERIVATIVE	MELTING POINT OF ISOMER, °C (3, 4, 5)		
	Meta	Ortho	Para
(h) Exceptions			
azophenol.....	205	172	216
aldehydobenzoic acid....	164-166	97-98	285
acetyltoluidide.....	303	296	306-307
hydroxyactanilide.....	149	203	168
acetylbenzoic acid.....	172	114-115	200
aminocinnamic acid.....	181-182	158-159	175-176
dihydroxybenzene.....	110	105	170
hydroxyazobenzene.....	114-116	82.5	155-156
nitrobenzaldehyde.....	58	40.9	106
methylnitrobenzoate.....	78.5	-8	96
ethylphenol.....	-4	< -18	46-47
nitrobenzonitrile.....	117-118	109-110	147-149
phthalic acid.....	347	231	sub. >300
hydroxydiphenyl.....	75-78	56-57	164-165
dimethylphthalate.....	67-68	0.0	140
chlorophenol.....	29	α , 7 β , 0.0 γ , -4	41
terphenyl.....	85	50	215
phthalic aldehyde.....	89-90	56	115-116

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THE PREPARATION AND PROPERTIES OF THE EIGHT DIASTEREOISOMERS OF 9,10,12,13-TETRAHY- DROXYSTEARIC ACID

A. F. MCKAY AND A. R. BADER

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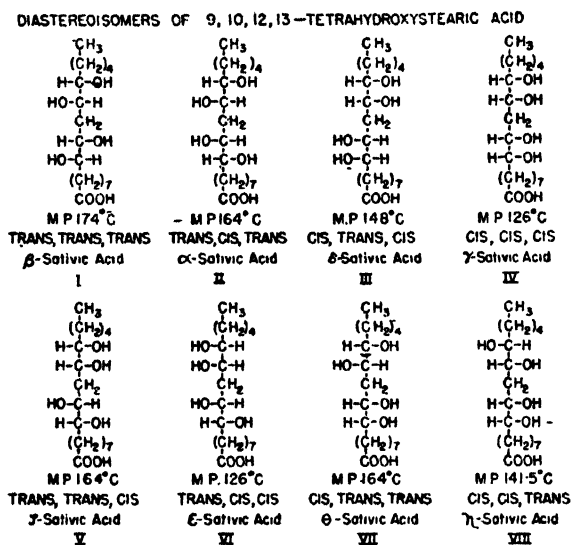
The eight diastereoisomers of 9,10,12,13-tetrahydroxystearic acid were prepared from α -linoleic acid (cis-9-cis-12-octadecadienoic acid). A new method of preparation was developed which establishes the spacial relationships of the hydroxyl groups in each diastereoisomer.

Hazura (1) was the first to isolate a 9,10,12,13-tetrahydroxystearic acid (sativic acid) from the alkaline potassium permanganate oxidation of linoleic acid. Further study (2-6) of this oxidation reaction resulted in methods for improving the yield and it is now established that two diastereoisomers of the tetrahydroxystearic acid are formed in this reaction. The melting points of these acids are 173° (I) and 164° (II). The more soluble one has also been reported to melt at 157-159°, but according to Riemenschneider *et al.* (7) this is an eutectic mixture of the α - and β -sativic¹ acids melting at 173° and 164°. Nicolet and Cox (8) obtained two different diastereoisomers of 9,10,12,13-tetrahydroxystearic acid by treating linoleic acid with hypochlorous and hypobromous acids to form the dichloro- and dibromo-dihydroxystearic acids. Replacement of the halogen atoms by hydroxyl groups gave two tetrahydroxystearic acids melting at 145° and 135°. Later work suggests that these acids are the same as the two diastereoisomers obtained in the peracetic acid oxidation of linoleic acid (9), or the alkaline potassium permanganate oxidation of linoleic acid (10) which are now described as melting at 146° (III) and 126° or 122° (IV). Kass and Burr (10) prepared a third set of diastereoisomers of 9,10,12,13-tetrahydroxystearic acid by the alkaline potassium permanganate oxidation of the trans-cis or cis-trans geometric isomer of linoleic acid. The melting points of these acids are given as 156-158° (V) and 126° (VI). The melting point of the former has now been raised to 164°. A seventh diastereoisomer of tetrahydroxystearic acid was re-

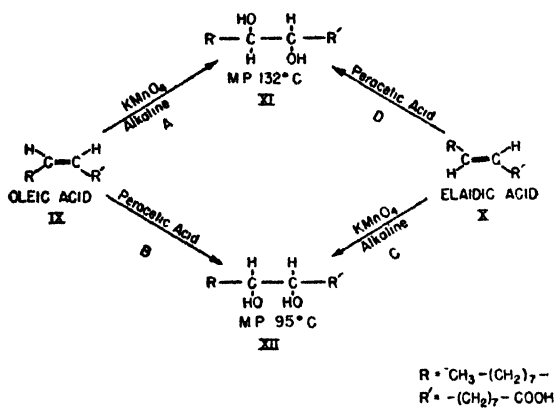
¹ The use of the name sativic acid for tetrahydroxystearic acid has led to a great deal of confusion in the study of the diastereoisomers of this acid. The main difficulty is that the terms α , β , γ etc., sativic acids give no indication of the structure of these compounds. Moreover the same Greek letters have been assigned to different diastereoisomers. Thus we propose that the system of nomenclature based on the use of the terms cis and trans be used to name these diastereoisomers. This system allows no misinterpretation of data and is more convenient for the correlation of experimental studies of these acids. In this method of naming the diastereoisomers of 9,10,12,13-tetrahydroxystearic acid three combinations of cis and trans are used *e.g.*, α -sativic acid becomes trans, cis, trans-9,10,12,13-tetrahydroxystearic acid. The first trans refers to the spacial relationship of the C₉ and C₁₀ hydroxyl groups, the cis refers to the relative configuration of the C₁₀ and C₁₂ hydroxyl groups and the final trans to the spacial interrelationship of the C₁₂ and C₁₃ hydroxyl groups. The eight diastereoisomers of 9,10,12,13-tetrahydroxystearic acid are given in formulas I-VIII, with this proposed system of nomenclature together with the sativic acid system.

ported by McKay, Jones, and Sinclair (11), which also melts at 164° (VII). In this report the eighth diastereoisomer (m.p. 141.5°) (VIII) is described.

If one considers the simpler case of 9,10-dihydroxystearic acid, then only two diastereoisomers are theoretically possible. 9-Octadecenoic acid exists in two geometric isomers, the *cis* form commonly known as oleic acid (IX) and the *trans*



Scheme A



Scheme B

form as elaidic acid (X). The two 9,10-dihydroxystearic acids melting at 132° (XI) and 95° (XII) are formed respectively by the alkaline potassium permanganate oxidation (A) and the peracetic acid oxidation (B) of oleic acid. In antithesis to this, the alkaline potassium permanganate (C) and peracetic acid (D) oxidations of elaidic acid (X) give the dihydroxystearic acids melting at 95° and 132° respectively. Infrared studies (12), and titration with lead tetraacetate (13) show the two hydroxyl groups in the higher-melting 9,10-dihydroxystearic

acid, to be trans to each other, and in the lower-melting diastereoisomer to be cis. Thus, alkaline potassium permanganate oxidation of a double bond supporting a cis configuration gives a trans α -glycol and vice versa. The opposite is true when peracetic acid is the oxidizing reagent. With these established facts in mind the eight diastereoisomers of 9,10,12,13-tetrahydroxystearic acid were prepared.

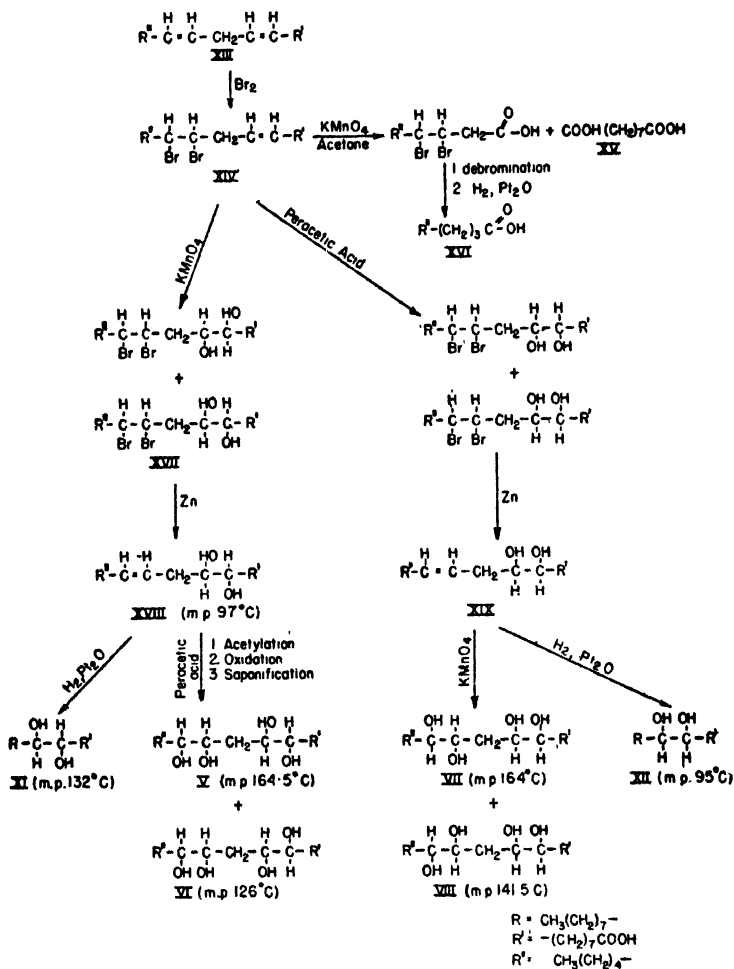
α -Linoleic acid (XIII) was brominated with slightly more than one molar equivalent of bromine at low temperatures (-15°). The desired dibromo derivative, 12,13-dibromo-9-octadecenoic acid (XIV) contained impurities of unchanged linoleic acid and 9,10,12,13-tetrabromostearic acid. The dibromination of linoleic acid and the oxidative degradation of the dibromo derivative have been reported by Toyama and Tutiya (14) without experimental details. In order to confirm the structure of 12,13-dibromo-9-octadecenoic acid, it was converted into its methyl ester (Iodine Value, 56.0), and then oxidized with potassium permanganate in acetone. The product, after debromination and hydrogenation gave azelaic acid (XV) in 78% yield and impure *n*-nonanoic acid (XVI) in 61% yield. These results prove that the double bond farther removed from the carboxyl group is preferentially brominated in the low temperature dibromination of α -linoleic acid.

Oxidation of 12,13-dibromo-9-octadecenoic acid with aqueous alkaline potassium permanganate solution gave a mixture of 9,10-dihydroxy-12,13-dibromostearic acids (XVII). Trans-9,10-dihydroxy-12-octadecenoic acid (m.p. 97° ; I.V., 80.6) (XVIII) was obtained from this product on debromination. Another set of reactions, in which 12,13-dibromo-9-octadecenoic acid was oxidized with peracetic acid and the product debrominated, saponified, and then distilled, gave an oil identified as cis-9,10-dihydroxy-12-octadecenoic acid (I.V., 80.2) (XIX). The structures of both the trans and cis-9,10-dihydroxy-12-octadecenoic acids were substantiated by reduction of these compounds to the corresponding 9,10-dihydroxystearic acids melting at 132° (XI) and 95° (XII) respectively. Nearly theoretical yields were obtained in each case.

The trans-9,10-dihydroxy-12-octadecenoic acid (XVIII) was acetylated and then oxidized with peracetic acid solution. After saponification of the product and acidification of the resulting alkaline solution, the free acids were obtained. These acids, on partition by solvents, gave two racemates of 9,10,12,13-tetrahydroxystearic acid in which the C_9 and C_{10} hydroxyl groups were trans and the C_{12} and C_{13} hydroxyl groups were cis. These diastereoisomers melted at 164° (V) and 126° (VI). The isomer having the C_{10} and C_{12} hydroxyl groups cis to each other was assigned the lower melting point. It is well known that in a set of cis, trans isomers the lower-melting, more soluble member has the cis configuration.

The fact that the spacial arrangement about the double bond was still cis in the trans-9,10-dihydroxy-12-octadecenoic acid was established on alkaline permanganate oxidation, when the two diastereoisomers of 9,10,12,13-tetrahydroxystearic acids melting at 174° (I) and 164° (II) were obtained. These are the acids obtained from linoleic acid on oxidation with this reagent.

Still another set of diastereoisomers of tetrahydroxystearic acid was prepared by the alkaline permanganate oxidation of *cis*-9,10-dihydroxy-12-octadecenoic acid (XIX). These acids melted at 164° (VII) and 141.5° (VIII). In these acids, the C₉ and C₁₀ hydroxyl groups are known to be *cis* to each other, and the C₁₂ and C₁₃ hydroxyl groups are known to be *trans* because of the method of prep-



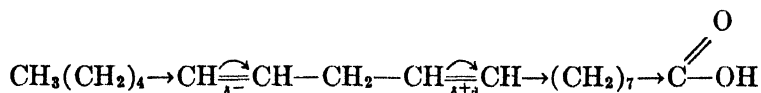
Scheme C

aration. If *cis*-9,10-dihydroxy-12-octadecenoic acid is acetylated and then oxidized with peracetic acid solution, the product on saponification gives the two diastereoisomers of 9,10,12,13-tetrahydroxystearic acid melting at 148° (III) and 126° (IV). These are identical with the two diastereoisomers prepared from linoleic acid by peracetic acid oxidation. Therefore the previous treatment of *cis*-9,10-dihydroxy-12-octadecenoic acid did not alter the configuration about the remaining double bond.

Riemenschneider *et al.* (7) concluded that bromination of *cis*-9-*cis*-12-octade-

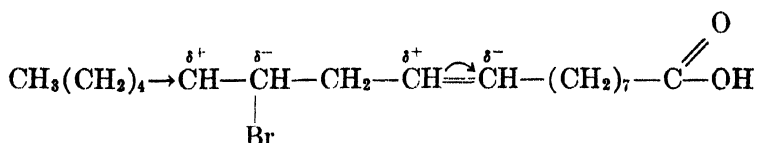
cadienoic acid would give two racemates of 9,10,12,13-tetrabromostearic acid. This conclusion was supported by previous observations that bromine adds to a double bond exclusively by *cis*-addition or by *trans*-addition. Applying the same arguments to the oxidation of α -linoleic acid, they concluded that alkaline potassium permanganate oxidation or peracetic acid oxidation would give only two racemates of 9,10,12,13-tetrahydroxystearic acid. The present work and the earlier studies of Toyama and Tutiya (14) clearly establish that bromine adds first to the C_{12} -double bond of linoleic acid, by the isolation and identification of 12,13-dibromo-9-octadecenoic acid from the products of its partial bromination. The stepwise addition of bromine to *cis*-9-*cis*-12-octadecadienoic acid becomes clear when considered in the light of the fundamental postulates of the English school regarding rates of reactions of olefins (15). Olefins are nucleophilic in character, and any substituent which increases the electron density of the ethylenic group increases its rate of reaction with electrophilic reagents. An electron

attractive group *e.g.*, $\text{C}=\text{O}$, —C=OR , OH , —C=O etc., will have the reverse effect. Thus, in α -linoleic acid there are present two opposing forces, the electron repulsive alkyl group attached to C_{13} and the electron attractive carboxyl group. The inductive effect of these groups may be represented as follows:



The electron attractive carboxyl group will have a greater effect on reducing the electron density of the 9-double bond than of the 12-double bond while the electron repulsive alkyl group will have a greater effect in increasing the electron density of the 12-double bond than of the 9-double bond. Both of these effects operate to increase the difference of the electron densities of the two double bonds giving the 12-double bond the stronger nucleophilic character. The $\text{—CH}_2\text{—}$ group between the two double bonds would aid in maintaining a potential difference. We have represented this by assigning the fractional charges δ^- and δ^+ to the ethylenic linkages as a whole rather than representing each ethylenic

linkage as a polar entity as is general procedure, *e.g.*, $\text{CH}_3 \rightarrow \text{CH}=\text{CH}_2$. Thus the attack of the electrophilic reagent :Br:^+ will be preferentially directed towards the 12-double bond. Once addition of this electrophilic reagent has occurred then the intermediate may be represented as:



and the polarity between the C_{12} and C_{13} positions must be greater than the polarity between the C_9 and C_{10} positions. This would then favor the addition

of the nucleophilic :Br:^- ion to C_{12} . The over-all effect of these electron shifts causing an increased reaction rate for the C_{12} -double bond over that of the C_9 -double bond. Besides the inductive effect of the carboxyl group one would expect a field effect to be operative. However, it is not possible to distinguish between the field and inductive effects.

The oxidation of linoleic acid may be explained also by use of these electronic mechanisms. Swern (16) has summarized the present knowledge of the per-acid oxidation of olefins, and electronically interpreted the effect of substituents on their rates of reactions. This interpretation may be applied equally well to linoleic acid oxidation with per-acids.

The stepwise method of preparation of the tetrahydroxystearic acids through the intermediate 12,13-dibromo-9-octadecenoic acid, has permitted the assignment of definite structures to the eight possible diastereoisomers. On the basis of these structures it is possible to predict the two diastereoisomers of 9,10,12,13-tetrahydroxystearic acid that would be obtained on alkaline potassium permanganate or peracetic acid oxidations of the geometric isomers of linoleic acid. Thus, Kass and Burr (10) must have obtained *cis*-9-*trans*-12-octadecadienoic acid on the partial elaidinization of α -linoleic acid rather than the *trans*-9-*cis*-12-octadecadienoic acid suggested, because only alkaline oxidation of the former would give the two diastereoisomers of tetrahydroxystearic acid melting at 156–158° (164°) and 126°.

The tetrahydroxystearic acids described in this paper were obtained as well-formed crystals with the exception of the two lowest-melting (126°) members of the series. The possibility of the existence of eutectic mixtures is realized and we are continuing with the studies of these acids.

EXPERIMENTAL

All melting points and boiling points are uncorrected.

Linoleic acid (XIII). α -Linoleic acid was prepared from corn oil through the tetrabromide by the method of McCutcheon (18). After debromination, the linoleic acid distilled in a vacuum (1 mm.) at 198–200°. The yield from the tetrabromostearic acid (m.p. 115°) was 88.9%, iodine value 180.8,² calc'd 181.0. Ultraviolet absorption analysis gave a specific α at 2340 Å of 87.2, while that reported by Mitchell and co-workers (19) for pure linoleic acid is 87.1.

12,13-Dibromo-9-octadecenoic acid (XIV). To a vigorously stirred solution of 31.2 g. (0.11 mole) of pure linoleic acid in 2700 cc. of petroleum ether cooled to 15°, a solution of 17.5 g. (0.11 mole) of bromine in 300 cc. of petroleum ether was added dropwise over a period of 2.5 hours. The reaction temperature was not allowed to go above –10°. At the end of the reaction, the solvent was removed *in vacuo* at ca. 35°. The last traces of solvent were removed by heating to 100° at a pressure of 1 mm. mercury. A viscous yellow oil (48.6 g.) remained.

Anal. Calc'd for $\text{C}_{18}\text{H}_{32}\text{Br}_2\text{O}_2$: Br, 36.32; Iodine Value, 57.60.

Found: Br, 37.92, 37.65; Iodine Value, 56.65.

Methyl ester of 12,13-dibromo-9-octadecenoic acid. The impure 12,13-dibromo-9-octa-

² The iodine values reported here were determined by the Rosenmund-Kuhnhehn method (17).

decenoic acid (39.0 g.; 0.088 mole) was dissolved in 250 cc. of methanol and 10 cc. of 4 N methanolic HCl was added. This solution was refluxed for two hours with the addition of 5-cc. portions of the methanolic HCl at half-hour intervals. The solution was then poured into two volumes of saturated brine. The organic layer was extracted with ether (3×150 cc.), the ethereal solution was washed with saturated brine (4×200 cc.), dried over sodium sulfate, and evaporated to dryness. The residue, an amber colored oil, was obtained in quantitative yield. This oil was distilled at a pressure of 0.5 mm.; the main fraction (b.p. 225–227°) was redistilled, and the intermediate fraction (b.p. 225°) taken for analysis.

Anal. Calc'd for $C_{19}H_{34}Br_2O_2$: Br, 35.3; Iodine Value, 55.8.

Found: Br, 34.92; Iodine Value, 56.0.

Oxidation of the methyl ester of 12,13-dibromo-9-octadecenoic acid with potassium permanganate in acetone. The following modification of Hilditch's (20) method was used for establishing the position of the double bond in the dibrominated linoleic acid. A suspension of sodium carbonate (2 g.) in 150 cc. of acetone containing 9.3 g. (0.02 mole) of methyl 12,13-dibromo-9-octadecenoate (I.V., 56.0) was stirred at -5° to 0° during the gradual addition of finely powdered $KMnO_4$. Twenty-seven grams of $KMnO_4$ was added before a permanent pink color was obtained. The acetone was removed by distillation and the residue extracted with hot methanol (3×100 cc.). After addition of zinc dust (10 g.) to the methanol solution, it was refluxed for one hour. The unreacted zinc and zinc bromide were filtered off and the combined filtrate and washings evaporated. The oily residue was saponified in 100 cc. of 3 N aqueous KOH by heating on the steam-bath for two hours. The clear soap solution was then poured into excess dilute hydrochloric acid and extracted with ether (3×100 cc.). This ethereal solution, after washing with saturated brine (4×100 cc.) and drying over sodium sulfate, was evaporated. A residual oil was obtained, which on solution in 50 cc. of ether deposited 3.01 g. (78.0% yield) of impure azelaic acid. Two crystallizations from water gave 2.1 g. of crystals melting at 104.5–105.5° alone and on admixture with an authentic sample of azelaic acid.

Evaporation of the ether from the original filtrate gave an oil which was dissolved in glacial acetic acid (50 cc.). This solution was treated with hydrogen in the presence of Adams platinum oxide catalyst (15 mg.) until the uptake of hydrogen ceased. The catalyst was filtered off and the filtrate was diluted with 6 volumes of water. The oil (1.98 g., 61.0% yield) could not be crystallized. Part (1 g.) of this impure *n*-nonanoic acid was converted to 2-*n*-octylbenzimidazole (m.p. 138.5–139.5°) by refluxing with *o*-phenylenediamine, as outlined by Pool, Harwood, and Ralston (21). They report the melting point 139.5–140.5°.

trans-9,10-Dihydroxy-12-octadecenoic acid (XVIII). 12,13-Dibromo-9-octadecenoic acid (39.0 g.; 0.088 mole) was oxidized in dilute alkaline solution with potassium permanganate by the method of Riemenschneider *et al.* (7). The product was recovered by extracting the decolorized and acidified permanganate solution with ether (3×400 cc.). The clear ether solution was washed with saturated brine solution until the aqueous solutions were neutral to Congo Red paper and dried over sodium sulfate. Evaporation of the ether left 38.6 g. of a light yellow oil consisting of a mixture of oxidation products, along with *trans*-9,10-dihydroxy-12,13-dibromooctadecanoic acid.

The crude oil (38.6 g.) was dissolved in methanol (500 cc.) and the solution cooled to 0° . Zinc dust (30 g.) was added slowly because at first the reaction was vigorous and exothermic. After the reaction had become quiescent, the reaction mixture was refluxed on a steam-bath for two hours. On cooling, the solid (zinc and zinc bromide) was removed by filtration and the methanolic filtrate was diluted with water (500 cc.) and a white waxy, lighter-than-water solid separated. This was filtered off, washed with petroleum ether and triturated with dilute HCl solution. The remaining white solid was washed with water and petroleum ether and dried. This solid proved to be impure *trans*-9,10-dihydroxy-12-octadecenoic acid (m.p. 86–92°), yield 4.0 g. or 14.8%. After two recrystallizations from 50% aqueous ethanol 2.1 g. of 9,10-*trans*-dihydroxy-12-octadecenoic acid was obtained as shiny plates melting sharply at 97°.

Anal. Calc'd for $C_{18}H_{34}O_4$: C, 68.75; H, 10.96; I. V., 80.6.

Found: C, 68.99; H, 11.25; I. V., 80.6.

trans-9,10-Dihydroxystearic acid from trans-9,10-dihydroxy-12-octadecenoic acid. The *trans-9,10-dihydroxy-12-octadecenoic acid* (100 mg., 0.0003 mole) was dissolved in glacial acetic acid (30 cc.) and hydrogenated in the presence of Adams platinum oxide catalyst (15 mg.). The product, recovered in the usual manner, melted at 125–128°, yield 98 mg. (97.4%). This was crystallized twice from 50% aqueous ethanol to yield 71 mg. of crystals melting at 132° alone and on admixture with a known sample of *trans-9,10-dihydroxystearic acid* (m. p. 132°).

Alkaline potassium permanganate oxidation of trans-9,10-dihydroxy-12-octadecenoic acid. Eighty-nine milligrams (0.00027 mole) of *trans-9,10-dihydroxy-12-octadecenoic acid* (m. p. 97°) was oxidized with aqueous alkaline permanganate solution using the method of Riemenschneider *et al.* (7). The crude product after filtration from the acidified and decolorized potassium permanganate solution melted at 138–149°, yield 55 mg., or 55.8%. This solid was extracted with acetone (3×1 cc.). The acetone-insoluble fraction, after one crystallization from 50% aqueous ethanol yielded 21 mg. of crystals melting at 173° (I). This melting point was not depressed by the diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 174°) obtained from the alkaline potassium permanganate oxidation of linoleic acid. The acetone extract, after removal of the acetone, was crystallized twice from 50% aqueous ethanol to give crystals melting sharply at 164° (II), yield 14 mg. The melting point of this compound was not depressed by the low-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 164°) obtained from the alkaline potassium permanganate oxidation of linoleic acid.

The acetylation and peracetic acid oxidation of trans-9,10-dihydroxy-12-octadecenoic acid. *Trans-9,10-dihydroxy-12-octadecenoic acid* (1.98 g. 0.006 mole) was dissolved in pyridine (5 cc.) and 1.08 g. (0.01 mole) of acetyl chloride was added dropwise to the pyridine solution cooled in an ice-water bath. After the exothermic reaction had subsided, the solution was allowed to stand at room temperature for twenty-four hours. It was poured into water (10 vols.) and extracted with ether (3×30 cc.). The ethereal extract was washed with dilute HCl to remove the pyridine, and with 10% brine until the aqueous washings were neutral to Congo Red. Evaporation of the ether left a light yellow oil.

This light yellow oil was further hydroxylated with peracetic acid solution using the conditions described by Swern *et al.* (22) for the hydroxylation of elaidic acid with peracetic acid; the only change was the use of three times the relative amount of H_2SO_4 . This was found to hasten the reaction considerably, and less time was required for the theoretical uptake of oxygen. The uptake of peroxide was followed by titration (23). At the end of the reaction period, the acetic acid solution was poured into water (10 vols.), and the oil which separated was recovered. This oil was saponified by heating with 3 *N* aqueous KOH solution (50 cc.) for one hour on a steam-bath. On pouring the cooled soap solution into ice-cold dilute HCl solution, a yellow precipitate (m. p. 90–97°) formed, yield 870 mg. This solid was extracted with boiling ethyl acetate (100 cc.). The unextracted material (92 mg., yield 8.5%) melted at 158–163°. Crystallization from 50% aqueous ethanol yielded rod-shaped crystals (65 mg.) melting at 164–164.5°.

Anal. Calc'd for $C_{18}H_{34}O_6$: C, 62.07; H, 10.34.

Found: C, 61.80; H, 10.32.

A mixed melting point determination with the known diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 164°) from the alkaline potassium permanganate oxidation of linoleic acid was depressed to 151–157°.

The ethyl acetate extract was cooled to 0°, when white crystals separated. These crystals melted at 141–145°, yield 22 mg. The ethyl acetate filtrate was evaporated to dryness and the remaining oil was dissolved in ether (20 cc.) and stored at –35° for three days. The ether solution deposited white crystals (50 mg.) which were filtered off, washed with ether, and dried, m. p. 75–103°. Fractional crystallization from ethyl acetate gave a crop

of crystals melting at 126° (3 mg.). This experiment was repeated to obtain more of these crystals melting at 126°.

Anal. Calc'd for $C_{18}H_{34}O_6$: C, 62.07; H, 10.34

Found: C, 62.21; H, 10.40.

The melting point of this compound was depressed to 110–115° on admixture with the low-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 126°) obtained by the peracetic acid oxidation of linoleic acid. The ether filtrate from the crystals melting at 75–103° was evaporated to dryness, and the remaining oil taken up in 3 *N* aqueous KOH (10 cc.) and poured into dilute HCl solution. To the milky suspension petroleum ether (10 cc.) was added and, the material left standing overnight in the refrigerator. The white crystals (22 mg.) which had formed at the interface were filtered off and dried. These crystals (m. p. 85–86°) are under investigation. A similar melting compound was found in the product from the peracetic acid oxidation of linoleic acid (12).

Peracetic acid oxidation of 12,13-dibromo-9-octadecenoic acid. Thirty-one grams (0.07 mole) of 12,13-dibromo-9-octadecenoic acid was hydroxylated with peracetic by the method already described. The oxidation was considered complete after two and a half hours. The reaction mixture was then poured into a saturated brine (8 vols.) to which 0.1 *N* sodium thiosulfate solution (3 cc.) had been added to remove the excess peroxide. The aqueous mixture was extracted with ether and the ether washed with saturated brine solution. Finally the ethereal extract was dried over anhydrous sodium sulfate and the ether evaporated. A light yellow oil remained, yield 31.4 g. This oil contained 9(10)-hydroxy-10(9)-acetoxy-12,13-dibromooctadecanoic acid, as well as other impurities. Several runs were made and 123.1 g. of yellow oil was collected. This oil was debrominated without further purification. The debromination was conducted as previously described and the product worked up in the same manner. The light yellow oil (81.6 g.) consisted of a mixture of 9(10)-hydroxy-10(9)-acetoxy-12-octadecenoic acid, linoleic acid, and lower oxidation products. This oil (I. V., 82.5, calc'd 80.6) was extracted with petroleum ether (6 × 100 cc.) to remove the linoleic acid, and the remaining clear oil (62.0 g.) was dissolved in acetone (350 cc.). The acetone was almost completely removed by distillation and the remaining solution was treated with petroleum ether when a white solid (0.3 g.) collected at the interface. It melted at 114–121° and after three crystallizations from 30% aqueous ethanol the melting point was raised to 124–126°. This melting point was not depressed when a sample was mixed with the low-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 126°) obtained from the peracetic acid oxidation of linoleic acid. The acid isolated here was formed by action of peracetic acid on the linoleic present as an impurity in the original 12,13-dibromo-9-octadecenoic acid. The petroleum ether was separated from the oily layer by decantation and the oil was extracted again with petroleum ether (12 × 50 cc.). The remaining oil had the iodine value 51.55, whereas the calculated iodine value for 9,10-dihydroxy-12-octadecenoic acid is 80.6. This oil was purified by converting it to the methyl ester as previously described and distillation. The methyl ester (37.8 g.; I. V., 48.2) was distilled at a pressure of ca. 0.5 mm. and a colorless fraction was collected at a vapor temperature of 186–188°. This fraction had the iodine value 73.2, calc'd 77.3. One more distillation, in which large first and last fractions were discarded, gave 8.8 g. of colorless oil, I. V., 76.5. This methyl ester of *cis*-9,10-dihydroxy-12-octadecenoic acid was then saponified in the usual manner to give a quantitative yield of *cis*-9,10-dihydroxy-12-octadecenoic acid, I. V., 80.2, calc'd 80.6.

cis-9,10-Dihydroxystearic acid from *cis*-9,10-dihydroxy-12-octadecenoic acid. The *cis*-9,10-dihydroxy-12-octadecenoic acid (0.276 g.; 0.0008 mole; I. V., 80.2) was dissolved in glacial acetic acid (30 cc.) and hydrogenated in the presence of Adams platinum oxide catalyst (15 mg.). After the uptake of hydrogen had ceased, the catalyst was removed by filtration and the acetic acid solution diluted with water (7 vols.). A white, flocculent precipitate (0.25 g., 93% yield) formed. This was filtered off, washed with water, and dried. The melting point 78–86° was raised to 94° by three crystallizations from ethanol, yield 184

mg. A sample of this compound on admixture with an authentic sample of *cis*-9,10-dihydroxystearic acid (m. p. 95°) gave no depression in melting point.

Acetylation of the cis-9,10-dihydroxy-12-octadecenoic acid and peracetic acid oxidation of the 9,10-diacetoxy-12-octadecenoic acid. *Cis*-9,10-dihydroxy-12-octadecenoic acid (1.95 g.; 0.0062 mole; I. V., 80.2) was acetylated by the method described for *trans*-9,10-dihydroxy-12-octadecenoic acid. The resulting oil was oxidized with peracetic acid in the usual manner. The oxidation product was a yellow oil which was saponified by heating on the steam-bath with 3 *N* aqueous KOH solution (100 cc.) for two hours. The soap was cooled, poured into ice-cold dilute HCl, and the waxy, yellow solid (1.47 g., 68.1% yield) filtered off. Trituration with ether (50 cc.) left white crystals (346 mg.), which were extracted with boiling acetone (6 × 10 cc.). The residual solid (91 mg.) after two crystallizations from 50% aqueous ethanol melted at 147–148° (III). A mixed melting point determination with a known sample of high-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 148°) obtained from the peracetic acid oxidation of linoleic acid was not depressed.

The combined acetone extracts on cooling gave 12 mg. of crystals which melted at 130–139°. The acetone filtrate was evaporated to dryness and again extracted with acetone (10 cc.). The acetone was evaporated off and the residue was crystallized twice from 50% aqueous ethanol to give 9 mg. of white amorphous solid (m. p. 125–126°) (IV). A mixed melting point determination with an authentic sample of the low-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid from the peracetic acid oxidation of linoleic acid was not depressed.

Alkaline potassium permanganate oxidation of cis-9,10-dihydroxy-12-octadecenoic acid. Three grams (0.009 mole) of *cis*-9,10-dihydroxy-12-octadecenoic acid (I. V. 80.2) was dissolved in 1.5% aqueous potassium hydroxide (300 cc.) and to the well-stirred solution 1% aqueous potassium permanganate (300 cc.) solution was added rapidly. After two minutes the reaction mixture was decolorized with sulfur dioxide, concentrated HCl (20 cc.) was added and the white waxy precipitate (2.10 g., 63.2% yield) was recovered by filtration. This solid was extracted with ether (180 cc.) which left white crystals (1.136 g.) melting at 131–142°. Extraction of the solid with boiling acetone (130 cc.) gave white crystals (276 mg.) which after two crystallizations from 50% aqueous ethanol melted sharply at 164°. This is the *cis*, *trans*, *trans*-9,10,12,13-tetrahydroxystearic acid (VII) and it depresses the mixed melting point to 150–158° on admixture with the *trans*, *cis*, *trans*-9,10,12,13-tetrahydroxystearic acid (II) from the alkaline potassium permanganate oxidation of linoleic acid. A mixed melting point determination between the *cis*, *trans*, *trans*-9,10,12,13-tetrahydroxystearic acid (m. p. 164°) (VII) and the *trans*, *trans*-*cis*-diastereoisomer (m. p. 165°) (V) gave on depression. However crystallographic studies show these two diastereoisomers to have different crystalline properties. The crystallographic data and infrared data will be published at a later date.

A sample of this new *cis*, *trans*, *trans*-9,10,12,13-tetrahydroxystearic acid (m. p. 164°) (VII) was submitted for analysis.

Anal. Calc'd for $C_{18}H_{34}O_8$: C, 62.07; H, 10.34.

Found: C, 61.93, 61.89; H, 10.64, 10.69.

The hot acetone extract from above was cooled to 0° and the crystals (25 mg.) which formed were filtered off and dried, m. p. 151–157°. Evaporation of the acetone left an oil which after trituration with ether deposited crystals (393 mg.) melting at 136–141°. Two crystallizations from 50% aqueous ethanol yielded 248 mg. of crystals melting at 144–148°. This material was extracted with boiling acetone (30 cc.), the acetone evaporated to dryness, and the remaining white amorphous solid crystallized twice from 50% aqueous ethanol. The resulting white shiny crystals (52 mg.) melted sharply at 141.5°. This compound (VIII) on admixture with the high-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 148°) (III) from the peracetic acid oxidation of linoleic acid melted at 135–138°.

Anal. Calc'd for $C_{18}H_{34}O_8$: C, 62.07; H, 10.34.

Found: C, 61.65; H, 10.54.

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SUMMARY

1. A method is described for the preparation of the eight diastereoisomers of 9,10,12,13-tetrahydroxystearic acid from α -linoleic acid. The special arrangements of the hydroxyl groups in each diastereoisomer are deduced from this method of preparation.

2. Two new fatty acids *cis*- and *trans*-9,10-dihydroxy-12-octadecenoic acid are also described.

3. The present system of nomenclature applied to the tetrahydroxystearic acids is discussed.

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OCCURRENCE OF STEARIC ACID IN BAYBERRY TALLOW (WAX)

A. F. McKAY

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Although Chevreul (1) reported the presence of stearic acid in bayberry tallow, later workers (2-4) have found no more than a trace. Sauer, Hain, and Boutwell (2) state that myristin and palmitin constitute 95% of the bayberry wax obtained from commercial supply houses. This wax is extracted from the berries of *Myrica cerifera*, a shrub common along the North American seacoast. Smith and Wade (3), using crystallization technique, were able to identify palmitin as a component of bayberry tallow, but concluded that stearic acid was not present. Jamieson, McKinney, and Gertler (4) examined the fat from the bayberries of *Myrica Mexicana* collected in Salvador, C.A. They reported that the fat had an iodine value of 1.2 (Hanus) and a saponification value of 216.7. It contained 1.3% oleic, 58% myristic, 35.6% palmitic, and a trace of stearic acid. Thus, in the use of a reputed sample of bayberry tallow for the preparation of myristic and palmitic acids, the author was surprised to find over 11% stearic acid present.

A sample of bayberry tallow was saponified and the acids liberated on acidification of the alkaline solution were methylated. The resulting mixture of methyl esters was fractionally distilled at a pressure of 30 mm. The methyl ester fractions obtained were further purified by crystallization from acetone. It proved more economical to purify the methyl esters before saponification to the fatty acids than to saponify the impure methyl ester fractions and then attempt to purify the free acids. The loss accompanying the purification by crystallization from acetone was much greater in the case of the fatty acids.

EXPERIMENTAL

Bayberry tallow. The bayberry tallow was supplied by Eimer and Amend, New York. It gave an iodine value of 0.00¹ and melted at 46-49°, soft 43° (capillary method).

Methyl esters of the fatty acids from bayberry tallow. Forty-five grams of KOH was dissolved in 250 cc. of hot 95% ethanol. To this solution, 102 g. of bayberry wax was added and heated at reflux temperature for twenty minutes. This alcoholic solution was diluted with 200 cc. of hot water and acidified with 200 cc. of 25% sulfuric acid. The aqueous layer was siphoned off and the fatty acid layer was washed with hot water (2 × 500 cc.). The fatty acid fraction was then dried by heating rapidly with stirring to 150°, yield 95 g.

The fatty acids were converted to their methyl esters in the usual manner (2) by refluxing with methanol containing 5% sulfuric acid (sp. gr. 1.84). The yield was almost quantitative.

Fractionation of methyl esters. A charge of 81.2 g. of the methyl esters was added to the still-pot and fractionated in a Todd (6) fractional distillation apparatus. The three-foot column (internal diameter 5 mm.) having the improved spiral wire packing was used. The distillation curve and operating conditions are given in Figure 1 and the fractions are described in Table I.

Purification of methyl ester fractions. The methyl myristate (m.p. 17.8°), methyl palmitate (m.p. 27.24°), and methyl stearate (m.p. 34.6°) fractions all melted a degree or two

¹ All iodine values were determined by the Rosemund-Kuhnhehn method (5).

below the corresponding pure esters. These melting points were easily raised by dissolving the methyl esters in acetone and cooling to 4°, when the crystalline methyl esters separated. The methyl myristate fraction (13.8 g.) on crystallization from 30 cc. of acetone melted at 18.58°, yield 8.8 g. The methyl palmitate fraction (31.1 g.), after two crystallizations from

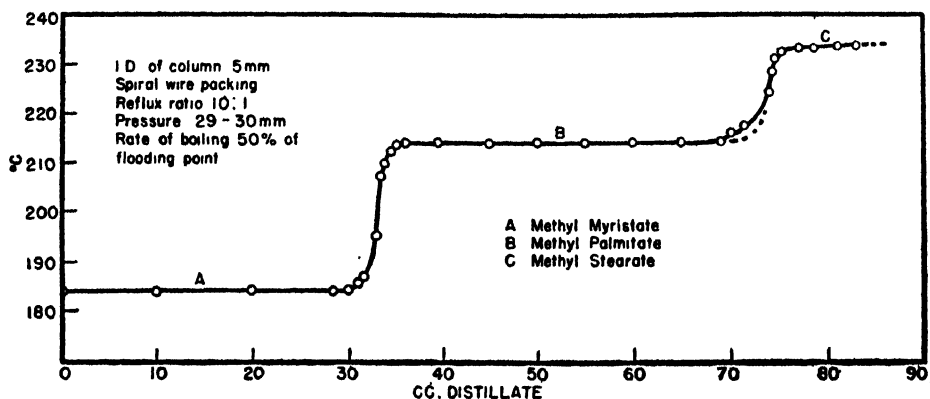


FIG. 1. FRACTIONATION OF METHYLATED FATTY ACIDS FROM BAYBERRY TALLOW

TABLE I
FRACTIONS FROM DISTILLATION OF METHYL ESTERS

NO.	WEIGHT IN GRAMS	PERCENT OF TOTAL	METHYL ESTER	M.P. °C	FINAL M.P. °C
1	24.8	30.6	Methyl myristate	17.8	18.58
2	2.8	3.4			
3	32.0	39.4	Methyl palmitate	27.2	29.60
4	4.2	5.2			
5	9.6	11.8	Methyl stearate	34.6	38.35
6	4.6	5.7	Residue		
Loss	3.2	3.9			

TABLE II
CONSTANTS OBTAINED FOR SATURATED ACIDS

FATTY ACID	M.P. °C	IODINE VALUE	ACID EQUIVALENT	
			found	calc'd
Myristic.. .. .	54.9	0.0	228.3	228.4
Palmitic.	63.0	0.0	256.3	256.4
Stearic	69.8	0.0	284.8	284.5

70-cc. portions of acetone, melted at 29.6° (melting point by capillary method 30-30.5°), yield 20 g. Similarly 11.8 g. of methyl stearate was crystallized three times from 32-cc. portions of acetone to give 5.6 g. of pure methyl stearate melting at 38.35°. (Melting point by capillary method 39-39.5°.)

² All melting points, unless otherwise stated, were obtained from melting point curves determined with the bulb of the thermometer and part of the stem immersed in the sample. The accuracy of the thermometer was $\pm 0.05^\circ\text{C}$.

Myristic, palmitic, and stearic acids. The free acids were obtained from the methyl esters by dissolving them in excess 4% ethanolic KOH and allowing to stand at room temperature for twelve hours. The free acids were then recovered by acidification of the diluted alkaline solution and filtration. The yields were quantitative. The white crystalline products were washed thoroughly with water and crystallized once from acetone to give pure myristic, palmitic, and stearic acids. The constants obtained for these acids are recorded in Table II.

This work was done as part of a program supported by a grant from the Ontario Cancer Treatment and Research Foundation to Professors R. N. Jones, Department of Chemistry and R. G. Sinclair, Department of Biochemistry, Queen's University.

SUMMARY

The presence of 11% stearic acid in bayberry tallow is reported along with the preparation of pure methyl myristate, methyl palmitate, methyl stearate, and the corresponding acids.

KINGSTON, CANADA

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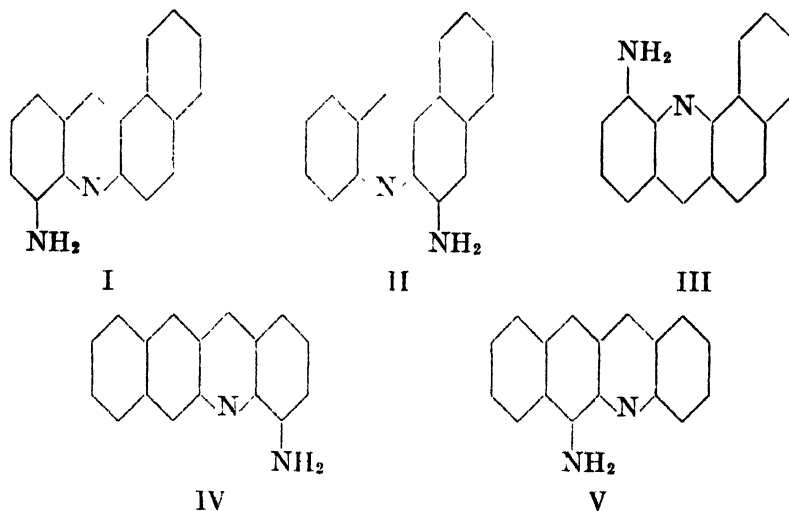
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FURTHER STUDIES OF AMINO BENZACRIDINES¹

G. BRYANT BACHMAN AND FRANK M. COWEN²

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In previous publications (1, 2) from this laboratory the preparation of a series of substituted aminobenzacridines was described. The present paper describes further members of this series of compounds with special emphasis on those in which the amine group is *peri* rather than *para* to the hetero nitrogen atom. The number of possible isomers is five.



Of these I and III were made in satisfactory yields, partial syntheses of IV and V were achieved, and II was not studied, before termination of the study of this series became necessary.

2-Bromo-3-nitrobenzoic acid condensed readily with 1- or 2-naphthylamine to give a 2-naphthylamino-3-nitrobenzoic acid which was readily cyclized with phosphorus oxychloride. The acridones so obtained were reduced by stannous chloride to the corresponding aminobenzacridones and by aluminum amalgam to the desired aminoacridines (I and III). Proof of the structure of the products was obtained by diazotization of the aminobenzacridones and conversion of them to triazolobenzacridones.

Compound IV was approached by condensing 3-amino-2-naphthoic acid with *o*-nitrobromobenzene and cyclizing the product with phosphorus oxychloride. The yields in this latter step were poor. The original condensation product also was reduced to 3-(*o*-aminophenylamino)-2-naphthoic acid. This gave a cyclic amide on heating, and the desired aminobenzacridone was not obtained.

Compound V was approached by coupling 3-phenylamino-2-naphthoic acid

¹ From the Ph.D. thesis of F. M. Cowen, Purdue University, June 1947.

² Present address: American Cyanamid Company, Stamford, Connecticut.

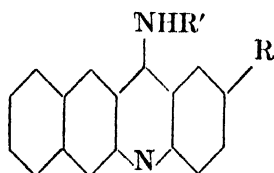
with benzene diazonium chloride, reducing the dye with sodium hydrosulfite, and cyclizing the resulting 4-amino-3-phenylamino-2-naphthoic acid with phosphorus pentoxide. Here again the yields in the last step were very poor, so poor in fact that insufficient material was obtained for an analysis. The diamino-naphthoic acid diazotized satisfactorily and gave a stable N-phenyltriazolonaphthoic acid.

All attempts to alkylate I or III with side chains common to antimalarials of the Plasmoguin type were unsuccessful. The amines were recovered unchanged from treatments of the following types:

- (a) Refluxing with γ -diethylaminopropyl chloride in benzene, butanol, or hexanol for fourteen hours.
- (b) Refluxing first with methylmagnesium iodide and then with γ -diethylaminopropyl chloride.
- (c) Refluxing with acrylonitrile (alone and with copper sulfate), or with 1-diethylamino-3-butanone, epichlorohydrin, or 2-chloro-1-nitroethane with or without solvents.

This surprising resistance to alkylation prevented us from obtaining compounds of a type suitable for antimalarial testing. It is hoped eventually to prepare a sodium derivative of I, or its *p*-toluenesulfonyl derivative and condense this with dialkylaminoalkyl halides.

Two new derivatives of 12-aminobenz(b)acridine (VI and VII) were also prepared



VI R = —H

R' = 6-methoxy-8-quinolyl

VII R = —OCH₃

R' = —(CH₂)₃N(C₂H₅)₂

by condensing 3-amino-2-naphthoic acid with aniline or anisidine, cyclizing the products with phosphorus oxychloride, and condensing the chlorobenzacridines so obtained with the appropriate side chain amine in phenol. Neither of these compounds showed antimalarial activity.

Acknowledgment. The authors are indebted to the Purdue Research Foundation and Eli Lilly and Company for financial support.

EXPERIMENTAL

Potassium 2-bromo-3-nitrobenzoate. The intermediate, potassium 2-bromo-3-nitrobenzoate, was prepared from 2-bromo-3-nitrobenzoic acid by the addition of aqueous potassium hydroxide solution to an alcoholic solution of the acid till just basic to phenolphthalein. Evaporation of the solvent gave the white salt. The bromonitrobenzoic acid was synthesized from 3-nitrophthalic acid according to the directions in *Organic Syntheses* (3).

2-(2'-Naphthyl)amino-3-nitrobenzoic acid (I-a). A mixture of 71 g. of potassium 2-bromo-3-nitrobenzoate, 105 g. of 2-naphthylamine, 18 g. of anhydrous potassium carbonate, 2 g. of precipitated copper, and 150 ml. of *n*-butanol was gradually heated with stirring to 110°. When the vigorous reaction had subsided, the solution was refluxed for two and three-fourths hours. The hot product was poured into 2.5 l. of cold water containing 10 g. of

potassium hydroxide, stirred, and filtered free of excess amine. The filtrate was acidified with concentrated hydrochloric acid and the precipitate filtered, washed with water, and dried. The greenish-yellow solid weighed 60 g. (78%) and was purified by two recrystallizations from dilute ethanol, reprecipitation from a basic solution, and recrystallization from glacial acetic acid. The yellow needles, m.p. 189–191°, were obtained in a 41% yield. A pure sample, obtained by several recrystallizations from dilute ethanol and methanol, melted at 190–192°.

Anal. Calc'd for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92.

Found: C, 66.34, 66.46; H, 3.91, 4.00.

2-(1'-Naphthyl)amino-3-nitrobenzoic acid (III-a). By a procedure similar to that used for the preparation of I-a, III-a was synthesized from potassium 2-bromo-3-nitrobenzoate and 1-naphthylamine. Care was needed to prevent too vigorous a reaction in the initial stages of the condensation. The crude acid, obtained in 62% yields, was purified by reprecipitation from a basic solution of the acid with dilute hydrochloric acid. The orange-yellow product, m.p. 200–212°, was pure enough for cyclization purposes. A sample recrystallized several times from dilute ethanol and dilute methanol gave light orange leaves, m.p. 219–220°.

Anal. Calc'd for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92.

Found: C, 66.22, 66.30; H, 3.93, 4.07.

3-Amino-2-(2'-naphthyl)aminobenzoic acid (I-b). A solution of 2 g. of I-a in 100 ml. of ethanol was reduced with hydrogen at three atmospheres and room temperature using 0.1 g. of platinum oxide (Adams) catalyst. When the calculated amount of hydrogen had been absorbed, the product was filtered free of catalyst, reduced in volume, and poured into an ice-water mixture. The solid product was recrystallized three times from dilute ethanol as slender, white needles, m.p. 216–218°.

Anal. Calc'd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07.

Found: C, 73.35, 73.25; H, 5.06, 4.99; N, 10.07, 10.01.

3-Amino-2-(1'-naphthyl)aminobenzoic acid (III-b). The reduction of III-a was carried out in a similar fashion to that of I-a. The crude product was purified by two recrystallizations from dilute ethanol and three recrystallizations from benzene-heptane. The light tan, leaf-like crystals melted at 153.5–154.5°.

Anal. Calc'd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07.

Found: C, 73.36, 73.46; H, 5.09, 5.18.

8-Nitro-12(?)-benz(a)acridone (I-c). A mixture of 80 g. of I-a and 360 ml. of phosphorus oxychloride was refluxed for two hours. The hot solution was poured into a mixture of 1500 g. of ice and 1.5 l. of concentrated, aqueous ammonia. The precipitate was filtered, washed with water, and hydrolyzed by suspension in boiling, dilute hydrochloric acid for one hour. The crude acridone was purified by dissolving it in a warm mixture of 1 liter of ethanol, 75 ml. of water, and 20 g. of sodium hydroxide, filtering the solution, and reprecipitating the acridone with excess dilute hydrochloric acid. The brownish-yellow precipitate, weighing 63 g. (84%), melted at 280–285°. A sample recrystallized three times from pyridine gave light orange needles, m.p. 293.5–294.5°.

Anal. Calc'd for $C_{17}H_{10}N_2O_2$: C, 70.34; H, 3.47; N, 9.65.

Found: C, 70.31, 70.42; H, 3.48, 3.55; N, 9.64, 9.71.

11-Nitro-7(12)-benz(c)acridone (III-c). By a similar procedure to that described above for the preparation of I-c, III-a was converted to III-c in 73% yields of reprecipitated product. In order to hydrolyze the chloronitrobenzacridine (III-d), it was necessary to reflux the suspension for nine hours in 6 N hydrochloric acid. A sample, recrystallized three times from pyridine, gave orange needles, m.p. 272–274°.

Anal. Calc'd for $C_{17}H_{10}N_2O_2$: C, 70.34; H, 3.47.

Found: C, 70.31, 70.42; H, 3.45, 3.40.

12-Chloro-8-nitrobenz(a)acridine (I-d). A mixture of 2.4 g. of I-c and 10 ml. of phosphorus oxychloride was refluxed two and one-half hours. The warm product was poured into a mixture of 75 ml. of concentrated, aqueous ammonia and 200 g. of ice. When the excess

phosphorus oxychloride had been destroyed, the suspension was extracted with chloroform; the chloroform extracts were dried and evaporated to dryness. The light yellow solid was crystallized from hot, dry benzene as 0.7 g. (27%) of long, slender, light yellow needles. One rapid recrystallization from dry benzene gave a compound melting at 218–219°. The product was dried *in vacuo* over phosphorus pentoxide, since it was readily hydrolyzed to the acridone (I-c) by moisture.

Anal. Calc'd for $C_{17}H_9ClN_2O_2$: Cl, 11.49. Found: Cl, 11.47, 11.56.

7-Chloro-11-nitrobenz(c)acridine (III-d). When III-c was refluxed with phosphorus oxychloride and isolated by a similar procedure to that employed for I-d, 2.4 g. (89%) of reddish-orange needles, crystallized once from benzene, was obtained. Two recrystallizations from the same solvent gave light yellow needles with a greenish fluorescence, m.p. 252.5–253.5°.

Anal. Calc'd for $C_{17}H_9ClN_2O_2$: C, 66.13; H, 2.94; Cl, 11.49.

Found: C, 66.09, 65.98; H, 2.94, 2.98; Cl, 11.50, 11.57.

8-Amino-12(7)benz(a)acridone (I-e). A suspension of 3.5 g. of I-c, 4.5 ml. of concentrated hydrochloric acid, and 14 ml. of ethanol was heated on a steam-bath for nine hours with a solution of 10.8 g. of stannous chloride dihydrate in 10.8 ml. of concentrated hydrochloric acid. The product was isolated according to the direction of Lehmkstedt and Schrader (4). Crystallization from pyridine gave 1.5 g. (48%) of glistening brown plates, m.p. 313–315° (d.). Recrystallization from ethanol gave yellow needles, m.p. 317–318° (d.).

Anal. Calc'd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76.

Found: C, 78.48; 78.38; H, 4.68; 4.77; N, 10.71, 10.60.

11-Amino-7(12)-benz(c)acridone (III-e). The preparation and isolation of III-e were accomplished by a procedure identical with that for the preparation of I-e but starting with III-c. The moist product was not purified but was used directly in the preparation of III-g. A small sample crystallized from ethanol as small yellow needles, m.p. 325–326° (d.).

Anal. Calc'd for $C_{17}H_{12}N_2O$: N, 10.76. Found: N, 10.53, 10.46.

13-Triazolo(fg)benz(a)acridone (I-f). The diazotization of 1 g. of I-e by the method of Lehmkstedt and Schrader gave 0.7 g. (67%) of flat leaf-like, light yellow crystals, crystallized from benzene. Recrystallization from this same solvent gave a compound melting at 226–228° (d.).

Anal. Calc'd for $C_{17}H_9N_3O$: C, 75.27; H, 3.34.

Found: C, 75.30, 75.39; H, 3.35, 3.30.

7-Triazolo(fg)benz(c)acridone (III-f). In a similar fashion 0.9 g. (60%) of III-f, crystallized from benzene, was obtained from 1.4 g. of III-e. Two recrystallizations from benzene gave light yellow, fibrous needles, m.p. 212–213° (d.).

Anal. Calc'd for $C_{17}H_9N_3O$: C, 75.27; H, 3.34.

Found: C, 75.14, 75.08; H, 3.40, 3.43.

8-Aminobenz(a)acridine (I). The reduction of 24.2 g. of I-c to 8-aminobenz(a)acridan and the subsequent oxidation to the acridine (I) was carried out by the method of Albert and Ritchie (5). A 100% excess of aluminum foil was used in the reduction. Only a few drops of 10% ferric chloride solution (oxidizing agent) were necessary, indicating complete, or almost complete, oxidation during the isolation of the product. The alcoholic extracts were reduced to a volume of 100 ml. and diluted with 750 ml. of water. The greenish-yellow precipitate (20 g.) was extracted with ether. The ether extracts were evaporated to dryness and extracted with ether. Removal of the solvent gave an orange-brown residue which was extracted with heptane. Evaporation of the heptane gave 1.5 g. (7%) of a solid which was recrystallized twice from ethanol as light yellow needles, m.p. 175–177°.

Anal. Calc'd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47.

Found: C, 83.60, 83.47; H, 4.94, 4.99; N, 11.46, 11.34.

The ether-insoluble fraction (13 g.) was recrystallized several times from dilute pyridine as light yellow plates, m.p. 315–317° (d.). An analysis indicated it was the aminoacridone (I-e).

Anal. Calc'd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76.

Found: C, 78.42, 78.53; H, 4.63, 4.68; N, 10.76, 10.84.

11-Aminobenz(c)acridine (III). Moist, crude III-e, obtained by the reduction of III-c with stannous chloride was reduced, as above, with aluminum-mercury amalgam. The oxidative step with 10% ferric chloride solution indicated that oxidation had been completed during isolation. The orange-yellow solid from two extractions with ether and heptane weighed 8.5 g. [32% based on the nitroacridone (III-c) used in the preliminary reduction]. Several recrystallizations from ethanol and heptane gave yellow, fibrous needles, m.p. 150–151°.

Anal. Calc'd for $C_{17}H_{13}N_2$: C, 83.58; H, 4.95; N, 11.47.

Found: C, 83.51, 83.38; H, 4.91, 4.81; N, 11.45, 11.31.

3-(2'-Nitrophenyl)amino-2-naphthoic acid (IV-a). A mixture of 12.5 g. of 3-amino-2-naphthoic acid (6), 50 g. of 2-bromonitrobenzene, 50 g. of anhydrous potassium carbonate, 0.15 g. of precipitated copper, and 120 ml. of cyclohexanol was refluxed, with stirring, for three hours at 150°. The dark red solution was poured into 1500 ml. of water containing 15 g. of potassium hydroxide. Cyclohexanol and unreacted 2-bromonitrobenzene were removed by steam distillation from the solution whose volume was maintained at about 1500 ml. by the occasional addition of water. Filtration and acidification of the filtrate with excess concentrated hydrochloric acid gave a brown precipitate which was filtered while hot (85°). The solid product was redissolved in a solution of 1500 ml. of water and 12 g. of sodium hydroxide, reprecipitated with excess concentrated hydrochloric acid, filtered white hot, and the filter cake washed with hot water till the washings were no longer acid. The reprecipitation process was repeated and an orange-brown precipitate obtained which weighed 53 g. (70% based on 2-bromonitrobenzene). The crude acid was readily purified by recrystallizations from glacial acetic acid and ethyl acetate. A pure sample, recrystallized several times from ethanol as orange needles, melted at 247–248°.

Anal. Calc'd for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09.

Found: C, 66.18, 66.31; H, 3.91, 4.00; N, 9.01, 8.96.

3-(2'-Aminophenyl)amino-2-naphthoic acid (IV-b). A mixture of 4.5 g. of IV-a, 10 ml. of ethanol, and 5.8 ml. of concentrated hydrochloric acid was heated on a steam-bath for six hours with a solution of 14 g. of stannous chloride dihydrate in 14 ml. of concentrated hydrochloric acid. The slurry was cooled, filtered free of excess acid liquors, and dissolved in 80 ml. of 2 *N* sodium hydroxide solution. After heating the solution for ten minutes on a steam-bath, it was acidified with glacial acetic acid. The suspension was made alkaline with concentrated, aqueous ammonia and filtered. The filter cake was washed with dilute ammonia and the washings added to the filtrate. Acetic acid was added to pH 6 and the yellow precipitate was filtered, washed with water, and dissolved in 500 ml. of ethanol. After treatment with Norit and concentration to a volume of 350 ml., the solution was allowed to cool. The yellow needles which deposited were added to those obtained by further concentration of the mother liquors for a total yield of 3.2 g. (89%). The product was purified by reprecipitation at pH 6 and two recrystallizations from methanol. The bright yellow needles melted at 219.5–220°, with the evolution of a gas, resolidified and remelted at 255–256°. This behavior can be attributed to the formation of the internal amide (IV-c).

Anal. Calc'd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07.

Found: C, 73.44, 73.48; H, 5.09, 5.04.

Internal amide of 3-N-(2'-aminophenyl)amino-2-naphthoic acid (IV-c). A small quantity of IV-b was heated in purified mineral oil to 230°. When foaming had ceased, the mixture was cooled and diluted with petroleum ether, and recrystallized once from dilute ethanol, once from petroleum ether-ethanol, and finally from methanol as bright yellow plates, m.p. 255.5–256.5°.

Anal. Calc'd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65.

Found: C, 78.45, 78.58; H, 4.79, 4.72.

4-Nitro-12(5)-benz(b)acridone (IV-d). A mixture of 1 g. of IV-a and 5 ml. of phosphorus oxychloride was refluxed for two hours. The hot solution was poured into an ice-concentrated aqueous ammonia mixture. When the excess phosphorus halides had been destroyed, the solid was removed and refluxed with dilute hydrochloric acid for two hours. The deep red precipitate was filtered, washed with water, and recrystallized twice from

dilute pyridine as 0.1 g. (11%) of beautiful dark red plates with a greenish fluorescence, m.p. 309–310°.

Anal. Calc'd for $C_{17}H_{10}N_2O_3$: C, 70.34; H, 3.47.

Found: C, 70.40, 70.47; H, 3.65, 3.69.

4-Amino-3-N-phenylamino-2-naphthoic acid (V-a). A solution of 9.6 g. of sulfanilic acid monohydrate, 3.5 g. of potassium carbonate, and 50 ml. of water was heated and stirred till all of the solid had dissolved. After cooling in an ice-bath to 15°, a solution of 3.7 g. of sodium nitrite in 10 ml. of water was added. The resulting solution was immediately poured into a well-stirred mixture of 10.6 ml. of concentrated hydrochloric acid and 60 g. of ice. The suspension was placed in an ice-bath for fifteen minutes. The mixture of the white diazonium salt was then poured into a previously prepared solution of 13.2 g. of VI-a, 19.1 g. of potassium carbonate, 100 ml. of water, 50 ml. of methanol, and 125 g. of cracked ice. The solution of the red dye was allowed to stand at room temperature for one hour, then heated to 45–50° and 23 g. of sodium hydrosulfite cautiously added. When all of the reducing agent had been added, the yellow-orange mixture was heated at 80° until foaming subsided. The product was cooled to room temperature and carefully acidified with 15 ml. of glacial acetic acid. The yellow precipitate was quickly filtered, washed with water, and dried *in vacuo*. The yield was 13 g. (94%) of a solid which readily oxidized on exposure to the air. The acid was analyzed as the monohydrochloride monoethanolate by treating an ether solution of V-a with excess hydrogen chloride and recrystallizing the solid three times from ethanol-isopropyl ether, as small, light yellow needles, m.p. 233–236°(d.). A gas was evolved above 150°.

Anal. Calc'd for $C_{17}H_{14}ClN_2O_2 \cdot C_2H_5OH$: C, 63.24; H, 5.87; Cl, 9.83

Found: C, 63.33, 63.43; H, 5.83, 5.78; Cl, 9.72, 9.65

3-Phenyl-naphtho(1,2)triazole-4-carboxylic acid (V-b) Crude V-a (5.6 g.) was dissolved in a warm solution of 3 g. of sodium bicarbonate and 1.6 g. of sodium nitrite in 200 ml. of water. The cooled mixture was treated with 35 ml. of concentrated hydrochloric acid, added dropwise over a period of fifteen minutes, and allowed to stand an additional fifteen minutes. Neutralization with sodium acetate gave a purple precipitate. The product was purified by reprecipitation and three recrystallizations from glacial acetic acid. The small, white needles melted at 325–327°(d.).

Anal. Calc'd for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83.

Found: C, 70.54, 70.42; H, 3.80, 3.85.

6-Amino-12(5)-benz(b)acridone (V-c). A solution of 13 g. of V-a and 43 ml. of 85% phosphoric acid was stirred at 100° while 110 g. of phosphorus pentoxide was added over a period of one-half hour. The temperature was allowed to rise to 155° during the addition and then heated at 150–160° for one-fourth hour. The viscous solution was poured into a mixture of 500 g. of ice and 600 ml. of concentrated, aqueous ammonia. The dark purple precipitate weighed 12.5 g. Continuous extraction of the product with 300 ml. of benzene gave a solution with a greenish fluorescence. The benzene solution was chromatographed on an aluminum oxide column and the column was developed with a 2:1 heptane-acetone mixture. The well-defined greenish-yellow layer was eluted with acetone and the acetone solution evaporated to dryness. Crystallization of the solid from ethanol gave small, brownish-yellow plates with a green fluorescence, m.p. 308–309°. There was not enough for an analysis.

3-N-Phenylamino-2-naphthoic acid (VI-a). A mixture of 280 g. (3 moles) of aniline and 167 g. (0.89 mole) of 3-hydroxy-2-naphthoic acid was refluxed for sixty-six hours. The cooled mixture was diluted with 100 ml. of ether and filtered. The yellow crystalline product was washed with ether. The washings and filtrate were combined, reduced in volume, and the recovered solid added to the above product. The powdered crude anilide was suspended in a warm solution of 1.5 l. of water and 40 g. of sodium hydroxide, filtered, and the moist filter cake treated with additional dilute sodium hydroxide solution, filtered, washed with water, and dried. The yellow, base-insoluble product weighed 130 g. (45%). A small sample recrystallized from glacial acetic acid gave greenish-yellow needles, m.p. 167–171°. Reported (7) 168–169.5°.

The anilide (106 g.) was hydrolyzed by refluxing the solid in a solution of 450 ml. of ethanol, 120 ml. of water, and 120 g. of potassium hydroxide for eight hours. The mixture was diluted with 3 l. of water, filtered, and the filtrate acidified with concentrated hydrochloric acid. The yellow solid, obtained in 97% yield (80 g.), was crystallized from ethanol as bright yellow needles, m.p. 239–241°. Four recrystallizations from four different solvents, ethanol, ethyl acetate, methanol, and benzene, gave light yellow needles, m.p. 239–240° (sintering at 236.5°). Reported by Schöpf *et al.* m.p. 235–237°.

Anal. Calc'd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98.

Found: C, 77.51, 77.62; H, 4.90, 4.84.

3-N-(4'-Methoxyphenyl)amino-2-naphthoic acid (VII-a). 3-Hydroxy-2-naphthoic acid was converted to 3-amino-2-naphthoic acid by the procedure described in Organic Syntheses. 3-Bromo-2-naphthoic acid was obtained from this acid by the method of Kenner *et al.* (8). The crude product was purified by solution in dilute sodium hydroxide, treatment with Norit, filtration, and reprecipitation with concentrated hydrochloric acid.

A mixture of 3.3 g. of 3-bromo-2-naphthoic acid, 10.2 g. of *p*-anisidine, 2.1 g. of anhydrous potassium carbonate, and 0.05 g. of copper powder was heated at 180–190° for two hours. The mixture was poured into cold water containing 1 g. of sodium hydroxide, allowed to stand till the excess anisidine had solidified, and filtered. The filtrate was acidified with concentrated hydrochloric acid and the yellow precipitate purified by reprecipitation and recrystallization from ethanol. The bright yellow needles (1.0 g., 26%) melted at 234–238° (sintering). A small sample recrystallized from ethanol, melted at 237–239°. Reported by Wilke (9), m.p. 240°.

Anal. Calc'd for $C_{18}H_{15}NO_2$: C, 73.70; H, 5.15.

Found: C, 73.63, 73.78; H, 5.24, 5.28.

12-Chlorobenz(b)acridine (VI-b). A mixture of 70 g. of VI-a and 390 g. of phosphorus oxychloride was refluxed for one and three-fourths hours. Most of the excess oxychloride was removed by distillation and the dark purple residue was poured into a mixture of ammonia, ice, and chloroform. When hydrolysis of the phosphorus oxychloride was complete, the chloroform solution was dried, filtered, and evaporated to dryness. The orange solid was recrystallized from dry benzene as 50 g. (71%) of orange-red needles, m.p. 174–175°. An analytical sample was prepared by two recrystallizations from benzene. The orange, fibrous needles melted at 173.5–174.5°. Reported by Schöpf (10), m.p. 165°.

Anal. Calc'd for $C_{17}H_{10}ClN$: C, 77.42; H, 3.82.

Found: C, 77.46, 77.32; H, 3.81, 3.88.

12-Chloro-2-methoxybenz(b)acridine (VII-b). By the same procedure described above, VII-a was converted to VII-b in 78% yields of once-crystallized product. A pure analytical sample, recrystallized from benzene as light orange, fibrous needles, melted at 211.5–212°.

Anal. Calc'd for $C_{17}H_{12}ClNO$: C, 73.59; H, 4.12; Cl, 12.07

Found: C, 73.59, 73.46; H, 4.13, 4.20; Cl, 12.04, 12.11.

5(12)-Benz(b)acridone (VI-c). A small quantity of VI-b was refluxed with dilute hydrochloric acid for one hour. The insoluble acridone was filtered, washed with water, and recrystallized three times from dilute pyridine as golden-yellow plates with a greenish fluorescence, m.p. 305–306°. Reported by Schöpf, m.p. 304–305°.

Anal. Calc'd for $C_{17}H_{10}NO$: C, 83.24; H, 4.52; N, 5.71.

Found: C, 83.25, 83.39; H, 4.52, 4.58; N, 5.69, 5.75.

2-Methoxy-5(12)-benz(b)acridone (VII-c). The hydrolysis of VII-b in a 3:1 mixture of glacial acetic acid and dilute hydrochloric acid was accomplished by refluxing the suspension for one hour. The orange-brown product was recrystallized three times from pyridine as orange plates with a greenish fluorescence, m.p. 335–337°. Reported by Wilke, m.p. 175°.

Anal. Calc'd for $C_{18}H_{12}NO_2$: C, 78.53; H, 4.76.

Found: C, 78.52, 78.63; H, 4.80, 4.86.

12-(6'-Methoxy-8'-quinolylamino)benz(b)acridine (VI). A mixture of 10 g. of VI-b, 7 g. of freshly distilled 8-amino-6-methoxyquinoline, and 30 g. of phenol was heated in an oil-bath at 105–115° for two hours. The dark red solution was poured into a solution of 25 g. of potassium hydroxide in 500 ml. of water. The orange solid was filtered, washed with

water, and crystallized from dilute pyridine as 12 g. (79%) of bright orange needles, m.p. 292-293°.

Anal. Calc'd for $C_{27}H_{19}NO_3$: C, 80.77; H, 4.77; N, 10.47.

Found: C, 80.75, 80.79; H, 4.80, 4.90; N, 10.45, 10.37.

12-(3'-Diethylamino-1'-propylamino)-2-methoxybenz(b)acridine (VII). Compound VII-b (7.4 g.) was heated in an oil-bath with 3.6 g. of 3-diethylamino-1-propylamine and 22 g. of phenol for one-half hour at 90-100°. The dark red solution was then heated at 100-110° for two hours. The cooled product was poured into a vigorously stirred solution of 25 g. of potassium hydroxide in 250 ml. of water and the gummy solid extracted with ether. The dry ether extracts were treated with hydrogen chloride until precipitation of the dark hydrochloride was complete. The gummy precipitate was crystallized from a mixture of ethanol, dioxane, and isopropyl ether as 5.3 g. (46%) of dark red crystals, m.p. 233°. Recrystallization from the same solvent mixture gave dark red, hygroscopic, minute crystals, m.p. 234-235° (d.), dried over phosphorus pentoxide *in vacuo* at 100°.

Anal. Calc'd for $C_{25}H_{31}Cl_2N_2O$: C, 65.21; H, 6.79.

Found: C, 64.97, 64.96; H, 6.65, 6.59.

SUMMARY

The preparation of various aminobenz(a, b, and c)acridines has been studied, especially with a view to obtaining the amino group in a peri rather than the para position to the hetero nitrogen atom.

LAFAYETTE, INDIANA

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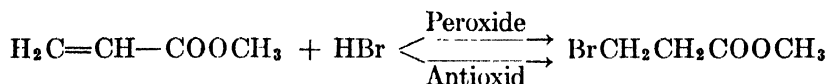
THE PEROXIDE EFFECT IN THE ADDITION OF REAGENTS TO UNSATURATED COMPOUNDS. XXVIII. THE ADDITION OF MERCAPTANS TO METHYL ACRYLATE

M. S. KHARASCH AND CHARLES F. FUCHS¹

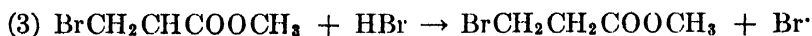
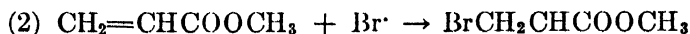
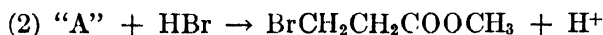
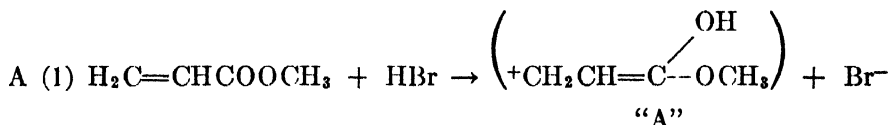
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INTRODUCTION

It has been shown that the so-called "normal" addition of hydrogen bromide to any type of unsaturated compounds may be reversed unless the double bond is conjugated with a carboxyl or a carbalkoxyl group (1). Specifically, methyl acrylate, (in the presence or absence of solvents), under both the most rigorous antioxidant and the most rigorous peroxidic conditions (1) (oxygen, ascaridol, light), gives the same product, methyl β -bromopropionate.



It is not known, however, whether the same compound is formed under these conditions by both of the mechanisms A and B indicated below, or by only one of them.



Unfortunately, since step B3 (see above) is very fast, it is impossible to determine whether both mechanisms operate in this reaction or whether the free-radical-chain reaction (B1,2,3) is inhibited and only the ionic type reaction (A1,2) is effective.

If hydrogen bromide were replaced by a reagent which requires a higher activation energy for step B3, it should be possible to demonstrate that the same addition product to methyl acrylate may be obtained by two different mechanisms when step B3 is slow; at the same time considerable amounts of other condensation products characteristic of a free-radical-chain mechanism should be formed. The addition of mercaptans to methyl acrylate was therefore investigated.

¹ Present address: Emulson Corporation, Chicago.

Apparently the "ionic" and "free radical" addition of mercaptans to methyl acrylate (and presumably to other compounds in which the double bond is conjugated with a carbalkoxyl group) yield the same product, but by two entirely different mechanisms. In these cases both the mercaptide ion (ionic addition) and the free mercaptide radical (free radical addition) add to the olefin to produce the ion or free radical of lowest energy content, *i.e.* the secondary ion or secondary free radical. This conclusion agrees with other observations on the addition of ions or free radicals to olefins.

EXPERIMENTAL PART

Addition of ethyl mercaptan to methyl acrylate in the presence of a peroxide and ultraviolet light. Methyl acrylate (10 g.), ethyl mercaptan (7.5 g.), and ascaridol (0.1 cc.) were mixed, placed in a quartz tube provided with a reflux condenser, and irradiated with ultraviolet light for 25 minutes. Since heat was evolved in the reaction, it was necessary, in order to avoid a rise in temperature beyond 40–50°, to cool the quartz flask with ice-water at frequent intervals. The reaction product was distilled at reduced pressure, and the following fractions were collected: Fraction I: 4.0 g., b.p. 90° at 745 mm. Fraction II: 6.3 g., b.p. 84° at 14 mm., n_D^{20} 1.4630. Fraction III: 3.2 g., b.p. 127–128° at 0.5 mm., n_D^{20} 1.4705. Fraction IV: Residue, 3.0 g., n_D^{20} 1.4745. Fraction I is a mixture of unreacted materials. Fraction II is the addition product of one molecule of ethyl mercaptan to one molecule of methyl acrylate, that is, methyl 2-thioethylpropionate. This compound was converted, by oxidation with 30% hydrogen peroxide in glacial acetic acid, to the sulfone of 2-thioethylpropionic acid (m.p. 112°). The recorded melting point of the sulfone is 112° (2). Fraction III is a compound formed by the condensation of one molecule of ethyl mercaptan with two molecules of methyl acrylate.

Anal. Calc'd for $C_{10}H_{18}O_4S$: C, 51.26; H, 7.75; S, 13.67. Mol. wt. 234.

Found: C, 51.71; H, 7.40; S, 13.50. Mol. wt. 232.

Fraction IV was not worked up. It is probably a compound formed from one molecule of ethyl mercaptan and three molecules of methyl acrylate. A corresponding compound was isolated in the study of the addition of propyl mercaptan to methyl acrylate.

The addition of ethyl mercaptan to methyl acrylate in the presence of a base. When methyl acrylate (50 g.) was mixed with pure ethyl mercaptan (36 g.), no reaction took place. However, when a very small quantity of trimethylbenzylammonium hydroxide (0.3 cc. of a 40% solution in H_2O) was added to the mixture, it soon became quite warm, and was cooled in ice-water. The reaction is complete in a short time. In the experiment here cited, the reaction mixture was allowed to stand for 12 hours at room temperature. By distillation at reduced pressure, a 95% yield of methyl 2-thioethylpropionate was obtained (b.p. 83.4/14 mm.; n_D^{20} 1.4628).

This substance was identical in every way with the material designated as Fraction II in the previous experiment, carried out by the addition of ethyl mercaptan to methyl acrylate in the presence of ultraviolet light and ascaridol. The sulfones obtained by the oxidation of the two esters with hydrogen peroxide (30%) in glacial acetic acid both melted at 112°, and gave no melting point depression.

Addition of propyl mercaptan to methyl acrylate in the presence of ascaridol and ultraviolet light. Two parallel experiments were conducted. Two quartz tubes were filled with mixtures of methyl acrylate (10 g.), propyl mercaptan (8.8 g.), and ascaridol (0.1 cc.). One tube (A) was sealed in air. The other tube (B) was cooled with liquid nitrogen and evacuated to 10^{-5} mm. Hg pressure. It was then allowed to warm to room temperature, cooled again with liquid nitrogen and once again evacuated to 10^{-5} mm. Hg pressure, to remove all oxygen. Both tubes were then warmed to 20° and irradiated (side by side) at room temperature with ultraviolet light. The temperature in both tubes rapidly rose to 50°. At that point, the illumination was interrupted, the tubes cooled to room temperature and the irradiation resumed. The total time of irradiation was 37 minutes. Both tubes were

opened and their contents subjected to distillation at reduced pressure and the following fractions were collected. Tube A (Air Present). Fraction I: 4.0 g., b.p. 37° at 151 mm. Fraction II: 7.0 g., b.p. 63° at 4 mm., n_D^{25} 1.4629. Fraction III: 1.0 g., b.p. 58° at 0.7 mm., n_D^{25} 1.4635. Fraction IV: 3.4 g., b.p. 120–123° at 0.8 mm., n_D^{25} 1.4692. Fraction V: 2.0 g., b.p. 150–155 at 0.8 mm., n_D^{25} 1.4699. Fraction VI: Residue: 1.0 g. Fraction II is the addition product of one molecule of propyl mercaptan to one molecule of methyl acrylate. Fraction IV is the addition product of one molecule of propyl mercaptan to two molecules of methyl acrylate.

Anal. Fraction IV. Calc'd for $C_{11}H_{20}O_4S$: S, 12.94; Mol. wt. 248.3.

Found: S, 13.40; Mol. wt. 241.

Tube B. (Air Absent). Fraction I: 3.9 g., b.p. 35° at 151 mm. (unreacted materials were collected in the cold trap). Fraction II: 6.0 g., b.p. 63° at 4 mm., n_D^{25} 1.4630. Fraction III: 1.6 g., b.p. 56° at 0.8 mm., n_D^{25} 1.4639. Fraction IV: 4.1 g., b.p. 118–123° at 0.8 mm., n_D^{25} 1.4699. Fraction V: 2.3 g., b.p. 150–156° at 0.8 mm., n_D^{25} 1.4719. Residue about 0.5 g.

Here [as well as in the experiment (A) in which air was present] Fraction II was shown to be methyl 2-thiopropylpropionate. Fraction IV corresponds to an addition product of one molecule of propyl mercaptan to two molecules of methyl acrylate. The probable formation of this compound is discussed in the theoretical part (D5).

Anal. Calc'd for $C_{11}H_{20}O_4S$: S, 12.94; Mol. wt. 248.3.

Found: S, 13.40; Mol. wt. 243.

Fraction V is probably a compound formed from one molecule of propyl mercaptan to three molecules of methyl acrylate (See D 7 in the theoretical part). The analyses indicate that the substance is contaminated with a small amount of the compound which occurs in Fraction IV.

Anal. Calc'd for $C_{15}H_{26}O_6S$: S, 9.60; Mol. wt. 334.

Found: S, 11.70; Mol. wt. 318.

Addition of lauryl mercaptan to methyl acrylate. Lauryl mercaptan (7.5 g.) and methyl acrylate (4.0 g.) were mixed in a glass-stoppered flask and 0.2 cc. of trimethylbenzylammonium hydroxide (40% solution in H_2O) was added. A vigorous, exothermic reaction took place. After the mixture had stood for one hour, 15 cc. of alcohol and 5 cc. of a 20% sodium hydroxide solution were added. The hydrolysis of the ester was rapid and accompanied by the evolution of heat. Upon addition of hydrochloric acid, the acid, 2-thiolaurylpropionic acid, separated. The yield of this acid was 95% of the amount calculated. It melted, after crystallization from methanol, at 61–62° (uncor).

By oxidation with 30% hydrogen peroxide, the 2-thiolaurylpropionic acid was readily converted to the sulfone, which, upon crystallization from acetic acid, melted at 137–138°. This sulfone is only moderately soluble in warm dilute alkali.

Anal. Calc'd for $C_{18}H_{34}O_4S_2$: C, 58.80; H, 9.88

Found: C, 58.36; H, 9.84.

SUMMARY

1. It has been established that mercaptans add to methyl acrylate by two different mechanisms: "ionic" and "free radical." The same addition product, $RSCH_2CH_2COOCH_3$ is obtained by both mechanisms.

2. The compound $RSCH_2CH_2COOCH_3$ is formed in 95% yield by the "ionic" addition of mercaptans to methyl acrylate.

3. In the free radical addition of mercaptans to methyl acrylate, there are formed, besides the substance $RSCH_2CH_2COOCH_3$, compounds which contain two, three (and even larger number) of methyl acrylate molecules per molecule of mercaptan.

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FACTORS INFLUENCING THE COURSE AND MECHANISM OF GRIGNARD REACTIONS. XIX. THE PREPARATION OF SUBSTITUTED BIBENZYLs FROM GRIGNARD REAGENTS, ALKYL HALIDES, AND ALKYL BENZENES, IN THE PRESENCE AND ABSENCE OF COBALTOUS CHLORIDE

M. S. KHARASCH AND W. H. URRY

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INTRODUCTION

It has been established in this Laboratory that the reaction of free methyl radicals with ether results in a gaseous mixture of a composition indicated in Example A, Table I. However, results have also been obtained which indicate that when free methyl radicals are generated from methylmagnesium bromide and some organic halides (in the presence of cobaltous chloride), they attack not only the solvent (ether), but the organic halide as well. This conclusion is based upon the following facts: (a) The larger amounts of methane formed in reactions B and C, Table I, than in reaction A; (b) the formation of high-boiling materials in reactions B and C, Table I, and none in reaction A.

To extend the knowledge of this side-reaction, and to attempt to put it to practical preparative use, cobaltous chloride-catalyzed reactions of Grignard reagents with alkyl halides were conducted in the presence of alkylbenzenes. These hydrocarbons were chosen because they do not react with Grignard reagents under ordinary conditions, and because a previous study (4) has shown that free methyl radicals react with them to give substituted bibenzyls. Isopropylbenzene was chosen as the most useful of these hydrocarbons because its reaction with free methyl radicals (generated by the decomposition of a diacetyl peroxide) gives almost pure 2,3-dimethyl-2,3-diphenylbutane.

Cobaltous chloride-catalyzed reactions of methylmagnesium bromide and methyl bromide in the presence of isopropylbenzene. In the first experiments, this reaction was carried out in the presence of about 500 ml. of ether. The results obtained are recorded in Table II. It is clear that at lower temperatures, the free methyl radicals attack predominantly the solvent ether, and the yield of 2,3-dimethyl-2,3-diphenylbutane is very small. However, when most of the ether was removed and the reaction temperature was increased to 100°, the yield of 2,3-dimethyl-2,3-diphenylbutane was increased to 23%, and, as was to be expected, the yield of methane was correspondingly larger than in the other experiments.

*Cobaltous chloride-catalyzed reactions of *n*-propylmagnesium bromide with *n*-propyl bromide in isopropylbenzene.* Somewhat better yields of 2,3-dimethyl-2,3-diphenylbutane were obtained when a solution of *n*-propylmagnesium bromide (ether removed) in isopropylbenzene, to which cobaltous chloride (6 mole %) had been added, was treated with a solution of *n*-propyl bromide in isopropylbenzene. At 35°, a yield of 25% of 2,3-dimethyl-2,3-diphenylbutane was obtained, and at 100°, 36%. The experimental details are recorded in Table III.

Thermal reactions of Grignard reagents with alkyl halides in isopropylbenzene solution at 100°. It was found (Table IV) that at 100°, Grignard reagents react

TABLE I
GAS COMPOSITION AND YIELD OF HIGHER-BOILING PRODUCTS IN REACTIONS OF METHYL-
MAGNESIUM BROMIDE WITH ORGANIC HALIDES IN THE PRESENCE OF COBALTOUS CHLORIDE

REACTANTS	YIELD OF HIGHER-BOILING PRODUCTS (%)	COMPOSITION OF GASEOUS PRODUCTS (%)		
		CH ₄	C ₂ H ₆	C ₂ H ₄
(A) C ₆ H ₅ MgBr + CH ₃ Br(1)	None	62	18	20
(B) CH ₃ MgBr + (CH ₃) ₂ CHCl(2)	6.0	85	9	6
(C) CH ₃ MgBr + C ₆ H ₅ CH ₂ CH ₂ CH ₂ Cl(3)	37.2	90	5	5

TABLE II
COBALTOUS CHLORIDE-CATALYZED REACTIONS OF METHYLMAGNESIUM BROMIDE WITH
METHYL BROMIDE IN THE PRESENCE OF ISOPROPYLBENZENE

REACTION WITH CH ₃ MgBr IN PRESENCE OF 6 MOLE % CoCl ₂	GRIGNARD REAGENT (MOLE)	i-PrC ₆ H ₅ (MOLES)	METHYL BROMIDE (MOLE)	GAS EVOLVED (MOLE)	YIELD DIMER ^a (%)	GAS ANALYSIS (%)		
						CH ₄	C ₂ H ₆	C ₂ H ₄
Solvent Et ₂ O present, 0°	1.21	2.65	1.09	1.51	1	68	16	16
Solvent Et ₂ O present, 35°	0.91	2.50	0.78	1.21	6.1	70	14	16
Solvent Et ₂ O removed, 0°	.84	2.45	.54	0.93	5	70	14	16
Solvent Et ₂ O removed, 35°	1.28	2.45	1.01	1.55	13	70	15	15
Solvent Et ₂ O removed, 100°	0.44	4.58	0.35	0.36	23	82	10	8

^a 2,3-Dimethyl-2,3-diphenylbutane

TABLE III
REACTIONS OF GRIGNARD REAGENTS WITH ALKYL HALIDES IN ISOPROPYLBENZENE
SOLUTION IN THE PRESENCE OF COBALTOUS CHLORIDE (6 MOLE %);
(ETHER REMOVED BY EVACUATION)

REACTIONS IN i-PrC ₆ H ₅	G. R. (MOLE)	i-PrC ₆ H ₅ (MOLES)	ALKYL HALIDE ^a (MOLE)	GAS EVOLVED (MOLE)	DIMER YIELD, %	GAS (C ₂ H ₆ :C ₂ H ₄ RATIO)
n-PrMgBr + n-PrBr, 35-40°	1.15	3.15	0.73	1.12	25	69:31
n-PrMgBr + n-PrBr, 100°	0.392	3.29	.368	0.714	32	65:35
n-PrMgBr + n-PrBr, 100°	.71	3.22	.58	1.04	31	86:14
n-PrMgBr + n-PrBr, 100°	.23	1.41	.205	0.41	36	66:34
MeMgBr + n-PrBr, 100°	.22	1.69	.194	.34	22	gas m. wt. ^c 28.6

^a Used in about 10% excess. Consumption of alkyl halide was determined by Volhard analysis.

^b Percentage of free radicals undergoing reaction with isopropylbenzene. The moles of free radicals are calculated by doubling the moles of n-propyl bromide consumed. The dimer is 2,3-dimethyl-2,3-diphenylbutane.

^c Gas contains propane, propylene, methane, ethane, ethylene.

readily with alkyl halides and isopropylbenzene to yield substantially the same products as are formed (Table III) at lower temperatures in the presence of cobaltous chloride. The yields of 2,3-dimethyl-2,3-diphenylbutane are, in gen-

eral, slightly lower than in analogous cobaltous chloride-catalyzed reactions. However, with isopropylmagnesium bromide, isopropyl bromide, and isopropylbenzene, the highest yield of dimer (2,3-dimethyl-2,3-diphenylbutane) yet observed in these types of reactions was obtained.

Methylmagnesium bromide, an alkyl halide, and isopropylbenzene do not yield any dimer (2,3-dimethyl-2,3-diphenylbutadiene) at 100° in the absence of cobaltous chloride or other catalysts of this type. Even at 150°, the reaction between methylmagnesium bromide and *n*-propyl bromide and isopropylbenzene is very slow—100 ml. of gas was evolved in six hours.

Cobaltous chloride-catalyzed reactions of methylmagnesium bromide in various solvents. The cobaltous chloride-catalyzed reaction of methylmagnesium bromide with methyl bromide in the presence of diphenylmethane gave a small yield of symmetrical tetraphenylethane. The same reaction in *p*-methoxy-*n*-propylbenzene solution gave 13% of an equimolecular mixture of meso and racemic hexesterol dimethyl ethers.

DISCUSSION

In previous publications from this Laboratory, we have described the preparation of substituted bibenzyls by two methods which involve free radicals as intermediates. These are illustrated below by a series of steps which lead to the formation of 2,3-dimethyl-2,3-diphenylbutane from isopropylbenzene and 2-chloro-2-phenylpropane, respectively.

- I. (a) $(\text{CH}_3\text{COO})_2 \rightarrow \text{CH}_3\cdot + \text{CO}_2 + \text{CH}_3\text{COO}\cdot$
 (b) $\text{CH}_3\cdot + \text{C}_6\text{H}_5(\text{CH}_3)_2\text{CH} \rightarrow \text{CH}_4 + \text{C}_6\text{H}_5(\text{CH}_3)_2\text{C}\cdot$
 (c) $2\text{C}_6\text{H}_5(\text{CH}_3)_2\text{C}\cdot \rightarrow \text{C}_6\text{H}_5(\text{CH}_3)_2\text{CC}(\text{CH}_3)_2\text{C}_6\text{H}_5$
- II. (a) $\text{CH}_3\text{MgCl} + \text{CoCl}_2 \rightarrow \text{CH}_3\text{CoCl} + \text{MgCl}_2$
 (b) $\text{CH}_3\text{CoCl} \rightarrow \text{CH}_3\cdot + \text{CoCl}\cdot$
 (c) $\text{C}_6\text{H}_5(\text{CH}_3)_2\text{CCl} + \text{CoCl}\cdot \rightarrow \text{C}_6\text{H}_5(\text{CH}_3)_2\text{C}\cdot + \text{CoCl}_2$
 (d) $2\text{C}_6\text{H}_5(\text{CH}_3)_2\text{C}\cdot \rightarrow \text{C}_6\text{H}_5(\text{CH}_3)_2\text{CC}(\text{CH}_3)_2\text{C}_6\text{H}_5$

A comparison of the intermediate products of the reactions postulated in I and II, suggested that if free radicals are actually generated in reaction II (b), then it should be possible to prepare substituted bibenzyls by the interaction of methylmagnesium bromide, methyl bromide, isopropylbenzene, and a small amount of cobaltous chloride or bromide. And such, indeed, was found to be the case. The formation of substituted bibenzyls from a mixture of such reagents may be represented by the following reactions:

- III. (a) $\text{CH}_3\text{MgBr} + \text{CoCl}_2 \rightarrow \text{CH}_3\text{CoCl} + \text{MgBrCl}$
 (b) $\text{CH}_3\text{CoCl} \rightarrow \text{CH}_3\cdot + \text{CoCl}\cdot$
 (c) $\text{CH}_3\text{Br} + \text{CoCl}\cdot \rightarrow \text{CH}_3\cdot + \text{CoBrCl}$
 (d) $\text{C}_6\text{H}_5(\text{CH}_3)_2\text{CH} + \text{CH}_3\cdot \rightarrow \text{CH}_4 + \text{C}_6\text{H}_5(\text{CH}_3)_2\text{C}\cdot$
 (e) $2\text{C}_6\text{H}_5(\text{CH}_3)_2\text{C}\cdot \rightarrow \text{C}_6\text{H}_5(\text{CH}_3)_2\text{CC}(\text{CH}_3)_2\text{C}_6\text{H}_5$
 (f) $\text{C}_2\text{H}_5\text{OC}_2\text{H}_5 + \text{CH}_3\cdot \rightarrow \text{gaseous products } (\text{CH}_4 + \text{C}_2\text{H}_6 + \text{C}_2\text{H}_4)^1$

¹ It has been shown that the formation of methane, ethane, and ethylene in the CoCl_2 -catalyzed reactions of methylmagnesium bromide with organic halides does not proceed by

However, the processes of formation of bibenzyls from acetyl peroxide and isopropylbenzene, as indicated in scheme I, and from the Grignard reagent and isopropylbenzene, as in scheme III, are not strictly comparable, although in both cases free methyl radicals are involved. Thus, in scheme I, the free methyl radicals react only with isopropylbenzene, while in the reaction proceeding according to scheme III, the free methyl radicals react not only with isopropylbenzene, but with the ethyl ether² as well III (f). It is, therefore, not surprising that, while the yield of the substituted bibenzyls from reaction scheme I is quantitative, on the basis of the reaction mechanism outlined, the yield of substituted bibenzyls is only 13% of the amount calculated on the basis of the reactions postulated in scheme III. An attempt to increase the yield of bibenzyls in scheme III by complete removal of the ether failed. No substituted bibenzyls were

TABLE IV
THERMAL REACTIONS OF GRIGNARD REAGENTS WITH ALKYL
HALIDES IN ISOPROPYLBENZENE SOLUTION AT 100°

REAGENTS (ETHER REMOVED)	GRIGNARD REAGENT (MOLE)	<i>i</i> -PrCH ₃ (MOLES)	ALKYL HALIDE ^a (MOLE)	GAS EVOLVED (MOLE)	DIMER YIELD ^b (%)	GAS (C ₁₀ H ₁₈ + 1; C ₁₀ H ₁₈ RATIO)
CH ₃ MgBr + CH ₃ Br.	0.44	4.38	c	No reaction in absence of CoCl ₂		
CH ₃ MgBr + <i>n</i> -C ₃ H ₇ Br.22	1.69	0.19	No reaction in absence of CoCl ₂		
C ₂ H ₅ MgBr + C ₂ H ₅ Br.276	2.68	.255	0.48	23	60:40
<i>n</i> -C ₂ H ₇ MgBr + <i>n</i> -C ₃ H ₇ Br.14	1.43	.13	.26	25	65:35
<i>i</i> -C ₃ H ₇ MgBr + <i>i</i> -C ₃ H ₇ Br.163	2.12	.116	.170	45	78:22

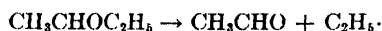
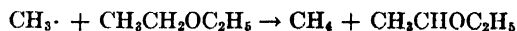
^a Used in about 10% excess. Consumption of alkyl halide was determined by Volhard analysis.

^b Percentage of free radicals undergoing reaction with isopropylbenzene. The moles of free radicals are calculated by doubling the moles of *n*-propyl bromide consumed. The dimer is 2,3-dimethyl-2,3-diphenylbutane.

^c Gas bubbled through solution.

formed in the complete absence of ether, possibly because of the insolubility of the Grignard reagent and the cobaltous chloride in the isopropylbenzene. Even

a mechanism of the type postulated by Evans and his co-workers [Evans and Lee, *J. Am. Chem. Soc.*, **56**, 654 (1934); Evans and Field, *J. Am. Chem. Soc.*, **58**, 720, 2284 (1936); Evans and Braithwaite, *J. Am. Chem. Soc.*, **61**, 898 (1939)] for the electrolysis of methylmagnesium iodide in ethers:



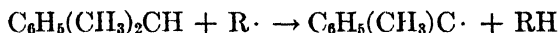
In studying the CoCl₂-catalyzed reaction of *n*-hexylmagnesium bromide with methyl bromide, a careful but unsuccessful search was made for octanol-2, the reaction product to be expected from the reaction of acetaldehyde with *n*-hexylmagnesium bromide.

² Another point of difference is that the peroxide reaction scheme I is homogeneous, while the Grignard reaction as in scheme III is, in part at least, heterogeneous.

at 100°, with a minimum of ether present, the yield of the 2,3-dimethyl-2,3-diphenylbutane was only 23%.

In order to decrease the loss of free radicals by attack on the ether molecules [reaction III (f)], the behavior of free propyl radicals on isopropylbenzene in ether solution was studied. We had previously established the following facts: (a) Free propyl radicals, generated by the decomposition of dibutyryl peroxide, react with isopropylbenzene to give propane (90%), propylene (10%), and a high yield (78%) of 2,3-dimethyl-2,3-diphenylbutane. (b) Free propyl radicals generated from propylmagnesium chloride, an alkyl halide, and cobaltous chloride, do not attack the ethyl ether-Grignard complex, but disproportionate to yield equal quantities of propane and propylene. In some respects, our predictions were confirmed. Thus, comparison of the results described in Tables II and III show that despite their lesser reactivity, and their tendency to disproportionate, the propyl radicals are somewhat more effective in their attack on isopropylbenzene (25%) than are free methyl radicals (13%) in the presence of ethyl ether.³

However, further consideration of the data disclosed that the improvement in the yield attained by using free propyl radicals cannot be due exclusively to the fact that the free propyl radicals do not attack ether molecules. Thus, we may infer, on the basis of the experimental evidence, that it is easier for a free propyl radical to remove the tertiary hydrogen atom of the isopropylbenzene molecule, than a hydrogen atom of the ether molecule.



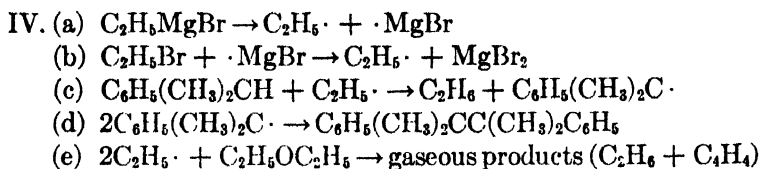
It should follow, therefore, that free methyl radicals, in the presence of large amounts of isopropylbenzene and some ether, should also attack extensively, if not preferentially, isopropylbenzene. Yet, at 35°, only about 13% of the free methyl radicals attacked the isopropylbenzene. Furthermore, it is to be noted that a higher percentage (*ca.* 64%) of the free propyl radicals, generated from propylmagnesium bromide, propyl bromide, and cobaltous chloride at 100°, undergo disproportionation (reaction 4, Table III) than free propyl radicals generated by the thermal decomposition of butyryl peroxide in isopropylbenzene at 125° (*ca.* 22%).

In our estimation, these divergent, apparently irreconcilable, results are best explained on the basis that the free radicals remain attached to the Grignard reagent-ether complex, and these react less readily with the hydrocarbon solvents than do the free radicals themselves. In other words, while it is permissible to compare the reactivity of hydrogen atoms in hydrocarbons toward free radicals, an additional mechanism must be taken into account if the activities of these hydrogen atoms are compared with the activity of hydrogen atoms in ethers in a medium containing a Grignard reagent. Furthermore, the temporary formation of free radical-Grignard reagent-ether complexes, may account for the extensive

³ A careful study of the results described in Table III discloses that at 100°, free propyl radicals are able to remove a hydrogen atom from ethyl ether. For example, in some experiments much less 2,3-dimethyl-2,3-diphenylbutane is obtained than would be expected from the yield of propane.

disproportionation of free propyl radicals in ether containing a Grignard reagent, as compared with the limited disproportionation of these free radicals in the presence of hydrocarbons which react readily with free radicals. It must also be borne in mind that the free radicals generated in the Grignard reaction in the presence of isopropylbenzene are generated in part at least at a liquid-solid interface, and that many of them could there disproportionate before they have an opportunity to escape into the solution and attack the hydrocarbon molecules.⁴

We have also noted that at 100°, in the presence of only small amounts of ether, and in the absence of cobaltous chloride, ethyl-, *n*-propyl-, and isopropylmagnesium bromides react with their respective halides and isopropylbenzene to yield the same products (gaseous, as well as 2,3-dimethyl-2,3-diphenylbutane) that are formed in the cobaltous chloride-catalyzed reactions at lower temperatures. Thus, for instance, the same ratio of propane to propylene (65% propane) is formed in the two cases. Upon this basis, these high-temperature reactions may also be looked upon as free-radical chain reactions (5).



Of the free radicals generated in this manner, the free isopropyl radical proved more effective in attacking isopropylbenzene (45%) than either the free propyl (25%) or the free ethyl (23%) radicals.

Whereas the steric factor involved can scarcely vary greatly among the three free radicals in reaction with the hydrocarbon, and whereas the reaction of free isopropyl radicals with isopropylbenzene is almost certainly not the one most favored from an energetic standpoint, it is reasonable to attribute this apparent superiority in reactivity of the free isopropyl radical not to reaction IV (C) above, but rather to the greater stability of the free isopropyl radical with respect to the competing disproportionation reaction in the presence of ether-Grignard reagent complex. Because of the lower reactivity of the isopropyl radical, it is to be expected that, in the absence of ether-Grignard reagent complex, higher yields of 2,3-dimethyl-2,3-diphenylbutane (and less disproportionation) should result from an attack of free ethyl or propyl radicals than from that of isopropyl radicals on isopropylbenzene, in spite of the greater stability at all times of the free isopropyl radical toward disproportionation.

The formation of free aliphatic radicals by the thermal decomposition of Grignard reagents in the presence of an alkyl halide is not applicable to the generation of free methyl radicals from either methylmagnesium chloride or methylmagnesium bromide.⁵ Thus, in the absence of cobaltous chloride, no reaction takes place when methyl bromide is bubbled through an isopropylbenzene-

⁴ This problem will be investigated later.

⁵ The formation of free methyl radicals from methylmagnesium iodide is discussed by Kharasch, Morrison, and Urry (6).

methylmagnesium bromide mixture held at 100°. The possibility that this unreactivity is due to insufficient solubility of methyl bromide in isopropylbenzene was disproved in two ways. First, it was found that reaction between methylmagnesium bromide, methyl bromide, and isopropylbenzene could be induced under these conditions, by periodic additions of small amounts of cobaltous chloride. Second, it was found that methylmagnesium bromide in isopropylbenzene does not react with *n*-propyl bromide at 100°. Even at 150°, the mixture reacted very slowly. The unreactivity, therefore, is attributable primarily to the stability of the methylmagnesium bromide under the experimental conditions imposed.

An interesting case where this thermal, free-radical reaction occurs with surprising ease is the reaction of ethylmagnesium bromide with cyclohexyl bromide. At the boiling point of that reaction mixture (about 40°), there is a steady evolution of gas (ethane, 54%; ethylene, 46%). A mixture of cyclohexane and cyclohexene (35% unsaturated) may be isolated from the reaction mixture.

Urion (7) had previously investigated the above reaction. He found that, when a solution of ethylmagnesium bromide and cyclohexyl bromide in ether is allowed to stand at room temperature, an exchange reaction takes place; he recovered 12% of cyclohexane. This exchange reaction has been confirmed in this Laboratory (8).

Urion further claimed that distillation of the ether from the reaction mixture removed ethyl bromide and caused a shift in the exchange equilibrium which gave him 40% of cyclohexane. This claim, however, is erroneous, since Urion failed to detect the presence of cyclohexene in his reaction. He also failed to note the evolution of ethane and ethylene.

EXPERIMENTAL PART

Reagents. Methyl-, ethyl-, *n*-propyl- and isopropyl-magnesium bromides were prepared according to the general method described by Kharasch, Morrison, and Urry. They were filtered through a coarse sintered-glass disc, and were titrated for Grignard reagent concentration and halogen content immediately before use.

Dow methyl bromide was used as such; ethyl bromide, *n*-propyl bromide, and isopropyl bromides were carefully distilled before use.

Anhydrous cobaltous chloride was prepared by heating the hydrated salt at 150° in a stream of dry hydrogen chloride.

Eastman's isopropylbenzene was distilled through a 100-plate Podbielniak column (b.p. 65.5° at 42 mm.; n_D^{20} , 1.4915).

p-Methoxy-*n*-propylbenzene was prepared by reduction of Eastman's anethole in ethyl alcohol over Raney nickel at 50 pounds pressure. It was purified by distillation through the 100-plate column (b.p. 76.5° at 6 mm.; n_D^{20} , 1.5040).

Eastman's diphenylmethane was sublimed *in vacuo* (m.p. 263–264°).

Eastman's cyclohexyl bromide was distilled through a 12-plate fractionating column (b.p. 79° at 48 mm.).

Typical procedure I. Cobaltous chloride-catalyzed reaction of methylmagnesium bromide with methyl bromide in ether-isopropylbenzene solution. A solution of methylmagnesium bromide (500 ml. of a 1.83 *N* ether solution; 0.91 mole) was placed in a dried nitrogen-swept Grignard reaction apparatus composed of a 1-liter, three-necked flask fitted through ground glass joints with a condenser, a Tru-Bore stirrer lubricated with heavy grease, and a dropping-funnel. Isopropylbenzene (300 g.; 2.50 moles) was added, and stirring was started.

The mixture was warmed to 35° and held there during the reaction. One-fourth of the cobaltous chloride to be used in the reaction (7.1 g.) was added at first, similar portions were added as the reaction progressed. Methyl bromide was bubbled into the reaction mixture at the rate of about 200 ml. per minute. Gas evolution began at once, and the gas mixture flowed through the condenser and a trap held at -80° into a water-filled gas reservoir. During the reaction, a total of 27.2 liters (S.C.) of gas was collected. This gas was analyzed by the method of Kharasch, Lewis, and Reynolds (1). It contained methane (70%), ethane (14%), and ethylene (16%).

When gas evolution ceased, the reaction mixture was treated with dilute acetic acid. The ether-isopropylbenzene layer was separated and washed with water, 10% sodium carbonate solution, and again with water and was dried over calcium chloride. The aqueous washings were diluted to a known volume, and an aliquot was analyzed for halide ion concentration by the Volhard method. From the calculated quantity of halide ion in the washings was subtracted the halide ion from the Grignard reagent and the cobaltous chloride used. The difference (0.78 mole) was the quantity of halide ion derived from the methyl bromide, and, therefore, a measure of the methyl bromide participating in the reaction.

Upon distillation of the ether solution, isopropylbenzene (290 g.; n_D^{20} 1.4915) was recovered. After the isopropylbenzene had distilled, a residue remained. Upon crystallization from 95% ethanol, eleven grams of 2,3-dimethyl-2,3-diphenylbutane, which melted at 118-119°, was obtained.

*Typical Procedure II. Cobaltous chloride-catalyzed reaction of *n*-propylmagnesium bromide with *n*-propyl bromide in isopropylbenzene.* Quantitative details are recorded in Table III, reaction 2. This procedure differed from the one described above in three ways. First, the ether solvent was removed; second, the cobaltous chloride (4 g) was added at the first of the reaction; and, third, a reaction temperature of 100° was maintained.

To remove the ether solvent, the Grignard reaction apparatus was evacuated through the condenser with the aid of a water aspirator pump while vigorous stirring was maintained. As the ether was removed, isopropylbenzene was slowly added through the dropping-funnel. The Grignard reagent separated as a white precipitate during this operation. After all the isopropylbenzene had been added and most of the ether had been removed, the mixture was held at 90° under water-pump vacuum for 1 hour.

Cobaltous chloride (4.0 grams) was added, and the mixture of *n*-propylmagnesium bromide and isopropylbenzene was then held at a temperature of 100° while a solution of *n*-propyl bromide in isopropylbenzene was dropped in over a period of 3 hours; gas evolution began at once. During the reaction, 16.0 liters (S.C.) of gas (m. wt. 44.5) was collected. Each successive 3-liter sample of gas collected was analyzed for unsaturation. Within the experimental error, all samples contained propane (65%) and propylene (35%).

After the gas evolution stopped, (ca. 4 hours) the reaction mixture was treated as in Procedure I. Distillation of the dried reaction mixture yielded first 10 ml. of ethyl ether that had remained in the reaction mixture. Isopropylbenzene (320 g.) was recovered, leaving a residue of 2,3-dimethyl-2,3-diphenylbutane (26.5 g.). The substance melted at 118-119°, after two crystallizations from 95% ethanol.

Typical Procedure III. Thermal reaction of isopropylmagnesium bromide with isopropyl bromide in isopropylbenzene. Quantitative data are given in Table IV, reaction 5. This experiment was conducted in the manner described in Procedure II except that no cobaltous chloride was used. Heating the reaction mixture for 12 hours at 100° was necessary to complete the reaction.

The reaction of ethylmagnesium bromide with cyclohexyl bromide. This reaction was conducted in a 1-liter, 3-necked flask fitted through ground glass joints with a dropping-funnel, a Tru-Bore stirrer, and a distilling head fitted with a down-draft condenser. Ethylmagnesium bromide (0.715 mole in 500 ml. of ether solution) and cyclohexyl bromide (116 g.; 0.70 mole) were placed in the reaction flask. The ether was slowly distilled by holding the reaction mixture at 46°. A slow gas evolution began with the distillation of the ether.

This gas was taken off through the distilling head, a condenser, a receiver, and a -80° trap into a gas reservoir. Gas evolution became more rapid as the ether was removed, and as the reaction temperature increased. After about two-thirds of the ether had distilled, 9 liters of gas, at standard conditions, had been collected and the reaction temperature reached 56° .

Suddenly, the reaction became very rapid, the remaining ether began to distill rapidly, and the rate of gas evolution increased. Even though the oil-bath surrounding the reaction vessel remained at 56° , the temperature at the still head reached 80° as the last liquid distilled. A total of 15 liters, at standard conditions, of gas collected (m. wt. 28.9; 46% unsaturated). It appeared to be an approximately equal mixture of ethane and ethylene.

All the distilled liquid was poured back into the reaction flask and the mixture was decomposed with dilute acetic acid. The ether solution was separated, washed with water, 10% sodium carbonate solution, and again with water, and dried over calcium chloride. A Volhard analysis of all aqueous washings indicated that the reaction was 93% complete.

Distillation of the ether solution yielded 41 grams of a mixture of cyclohexene and cyclohexane (b.p. $78-80^{\circ}$) which was found to be 35% unsaturated. Ten grams of cyclohexyl bromide was recovered.

SUMMARY

1. At low temperatures, ($0-20^{\circ}$), Grignard reagents in the presence of cobaltous chloride, an alkyl halide, and alkylbenzenes give rise to substituted bibenzyls.

2. Bibenzyls were also obtained by adding alkyl halides to a mixture of a Grignard reagent (other than methyl) and an alkylbenzene at 100° .

3. Since the same substituted bibenzyls are also produced by the decomposition of acetyl peroxide in alkylbenzene solutions, the reaction mechanisms proposing free alkyl radicals as intermediates in both reactions are supported.

4. A discussion of the factors influencing these reactions, and of the reaction mechanism is included.

CHICAGO, ILL.

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THE PHOTOSYNTHESIS OF SEMI-MUSTARD GAS, 2-CHLOROETHYL-2-HYDROXYETHYL SULFIDE¹WALTER H. C. RUEGGERBERG, WALTER A. COOK,² AND E. EMMET REID*Received August 22, 1947*

The compound 2-chloroethyl-2-hydroxyethyl sulfide, commonly referred to as semi-mustard gas, or simply as semi-H, is known to be an intermediate in the hydrolysis of mustard gas (1). Ogston (2), as well as Woodward and Owens (3) have isolated this compound after hydrolyzing mustard gas or one of its analogs.

At the time this work was done, a method for the synthesis of semi-H had not been reported in the published chemical literature (see footnote 1). Since then, Fuson and Ziegler (4) have reported the photochemical combination of ethanolmercaptan and vinyl chloride, while Grant and Kinsey (5) prepared semi-H by treating thiodiglycol with thionyl chloride in chloroform. Apparently, the work of Fuson and Ziegler (4) was performed while this work was in progress.

Prior to the appearances of the papers by Fuson and Ziegler and Grant and Kinsey, it appeared advisable to prepare semi-H by the novel reaction consisting in the photochemical addition of ethanolmercaptan to vinyl chloride:



The method used was an adaptation of that first developed by Vaughn and Rust (6) and later by Salzberg, Ellingboe and Lazier (7) and others (8).

Two methods were worked out for effecting the photochemical condensation of ethanolmercaptan to vinyl chloride. In the first method, vinyl chloride was absorbed at atmospheric pressure in a mixture consisting of the mercaptan and an inert solvent such as methanol or benzene under constant irradiation from a 100-watt CH4 mercury vapor lamp as supplied by the General Electric Company. The solvents employed in this particular process should be capable of dissolving both reagents and product, and in addition should transmit the ultraviolet radiation down to about 3000 Å. This reaction is carried out at about 20-25°.

In the second, the preferred method, the photo-condensation was carried out using liquid vinyl chloride and ethanol mercaptan in sealed tubes. The mixtures so prepared were irradiated under water by means of an S-4 mercury vapor lamp. Since no inert solvent is used in this process, it is only necessary to open the tubes and allow excess vinyl chloride to escape. This procedure is superior insofar as that the reaction rate is faster and purification by distillation of the solvent is unnecessary.

¹ The work here reported was completed early in 1944; however, due to security reasons, publication was delayed. In the interim, Fuson and Ziegler (see reference 4) have published their results of the photosynthesis of semi-mustard gas from mercaptoethanol and vinyl chloride. Although these authors employed essentially the same reaction, the work described in this paper deals with the same synthesis under different conditions, indicating at the same time the rate of the reaction. The permission of the Chief, Chemical Corps has been granted for the publication of this article.

² Present address: University of Akron, Akron, Ohio.

TABLE I
FORMATION OF SEMI-H IN BENZENE AT ATMOSPHERIC PRESSURE^a

EXPT NO.	AMYL DISULFIDE CATALYST, G.	IRRADIATION TIME, MIN.	MAXIMUM RE- ACTOR TEMPER- ATURE, °C.	WEIGHT OF PRODUCT, G.	UNREACTED MERCAPTAN, %	CONVERSION OF ETHANOLMER- CAPTAN TO SEMI- H, %
1	0.0	60	19.5	312.9	11.77	55.0
2	.84	60	22.0	338.5	3.96	88.6
3	.84	60	23.0	333.9	4.25	82.7
4 ^b	.84	60	22.0	227.1	4.81	86.7

^a Quantity of reagents indicated in text. Ethanolmercaptan purity 98%.

^b Only 100 ml. benzene used in this run. Product was cloudy.

TABLE II
FORMATION OF SEMI-H IN METHANOL AT ATMOSPHERIC PRESSURE^a

EXPT. NO.	CATALYST, G.	IRRADIATION TIME, MIN.	MAXIMUM REACTOR TEMP., °C.	WT. OF PRODUCT, G.	UNREACTED MERCAPTAN, %	CONVERSION OF ETHANOL- MERCAPTAN TO SEMI-H, %
1	0.85 g. amyl disulfide	15	16.0	265.1	24.26	21.1
2	.85 g. amyl disulfide	30	18.5	280.0	14.14	50.6
3	.85 g. amyl disulfide	45	20.0	305.8	4.17	84.4
4	.85 g. amyl disulfide	60	22.0	318.3	0.10	99.6
5	.85 g. amyl disulfide	75	20.5	320.9	0.07	99.7 ^b
6	.85 g. amyl disulfide	90	21.0	316.5	0.01	99.9 ^c
7	.0	45	19.5	294.7	10.13	63.5
8	.0	60	19.0	300.4	3.23	88.5

^a Quantity of reagents indicated in text. Ethanolmercaptan purity 98.0%.

^b Product turbid at end of reaction

^c Insoluble solid separated. Analysis showed this material to contain 53.12% chlorine approximating the theoretical chlorine content of 65.71% for polyvinyl chloride.

TABLE III
FORMATION OF SEMI-H IN METHANOL AT ATMOSPHERIC PRESSURE
USING PURIFIED ETHANOLMERCAPTAN^a

EXPT. NO.	AMYL DISULFIDE CATALYST G.	IRRADIATION TIME, MIN.	MAXIMUM RE- ACTOR TEMP., °C.	WT. OF PRODUCT, G	UNREACTED MERCAPTAN, %	CONVERSION OF ETHANOLMER- CAPTAN TO SEMI- H, %
1	0.0	45	19.0	289.8	5.76	80.0
2	.0	60	22.0	310.1	1.15	95.7
3	.85	30	19.5	276.6	15.00	50.3
4	.85	45	22.0	307.8	2.20	91.9
5	.85	60	22.0	307.0	0.08	99.7

^a Quantity of reagents indicated in text. Ethanolmercaptan purity 99.8%.

It has been shown previously (8), that a trace of amyl disulfide is a catalyst or perhaps better, a reaction promoter, for the photo-addition of mercaptans to vinyl chloride. As seen from the results in Tables I to V, amyl disulfide acts catalytically in the initial reaction period. Although disulfides boost the reac-

tion rate, they are not essential unless reaction inhibitors such as sulfur or copper are present. These facts, together with other evidence (9), led to the formulation

TABLE IV
FORMATION OF SEMI-H IN SEALED TUBES USING 98.0% PURE ETHANOLMERCAPTAN^a

EXPT. NO.	AMYL DISULFIDE CATALYST, G.	IRRADIATION TIME, MIN.	WT. OF PRODUCT, ^b G.	UNREACTED MERCAPTAN, %	CONVERSION OF ETHANOLMERCAPTAN TO SEMI-H, %
1	0.0	2	5.116	48.03	33.9
2	.0	5	6.519	14.33	71.1
3	.0	10	7.262	5.30	87.6
4	.0	15	7.428	3.67	91.2
5	.0	20	7.783	1.51	97.6
6	.0	25	8.019	0.45	101.7 ^c
7	.045	2	6.060	21.55	60.6
8	.046	5	6.969	8.46	80.7
9	.046	10	7.919	1.08	99.2
10	.046	20	7.930	0.83	99.5

^a Quantity of reagents indicated in text.

^b After degassing and evacuating.

^c Anal. calc'd for C₄H₉ClOS: Cl, 25.22; S, 22.81.

Found: Cl, 24.66, 25.09; S, 22.20, 22.26.

TABLE V
FORMATION OF SEMI-H IN SEALED TUBES USING 99.8% PURE ETHANOLMERCAPTAN^a

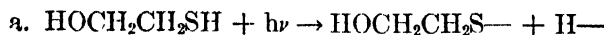
EXPT. NO.	AMYL DISULFIDE CATALYST, G.	IRRADIATION TIME, MIN.	WT. OF PRODUCT, G.	UNREACTED MERCAPTAN, %	CONVERSION OF ETHANOLMERCAPTAN TO SEMI-H, % ^a
1	0.0	2	5.684	43.66	40.0
2	.0	5	6.648	21.25	65.4
3	.0	10	7.466	6.61	87.1
4	.0	15	7.387	10.20	82.9
5	.0	20	7.685	4.66	91.5
6	.053	2	6.119	32.23	51.2
7	.046	5	7.153	12.60	77.5
8	.045	10	7.707	5.21	92.0
9	.046	15	8.007	1.44	98.0
10	.046	25	8.241	0.20	102.2 ^b

^a Quantity of reagents indicated in text.

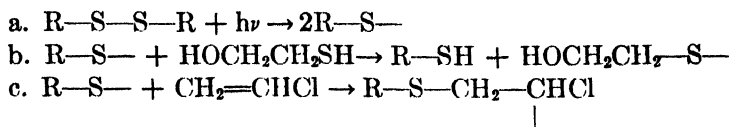
^b Anal. Calc'd for C₄H₉ClOS: Cl, 25.22; S, 22.81.

Found: Cl, 25.09; S, 22.96.

of an over-all reaction mechanism in the case of the disulfide-free reaction, which is postulated to be of a free radical chain nature:

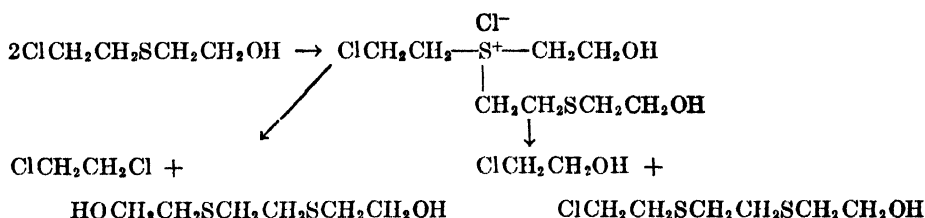


It has been shown that disulfides dissociate into thioalkyl radicals when irradiated with light of wavelengths longer than those required to rupture or excite the S—H bond (10). This fact suggests that disulfides, such as amyl disulfide used in this work, will initiate a chain more readily by breaking into two alkylthio radicals which, from the above mechanism, are recognized to be the chain carriers. The initial phases of the disulfide catalyzed chain are represented as follows:

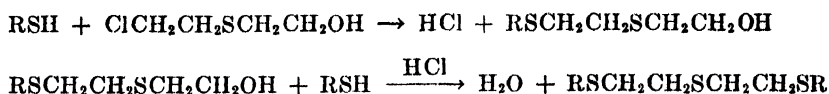


Although isolation of the semi-H produced either by the solvent method at atmospheric pressure or by the liquid vinyl chloride-sealed tube method is quite simple, the distillation of the product even at one mm. Hg pressure was accompanied by deterioration. It has already been pointed out that semi-H hydrolyzes very much more rapidly than mustard gas itself (1), thus indicating the greater reactivity of the residual chlorine atom in semi-H as compared with mustard. Ogston (2) attributes much of the instability of semi-H to the formation of sulfonium complexes with subsequent decomposition. Similar beliefs are presently held by Fuson and Ziegler (4) and Bell, Bennett, and Hock (11). As a result of the present investigation, it is believed that the decomposition of semi-H follows two courses, namely, the formation of sulfonium complexes, as pointed out by Ogston, and the reaction of semi-H with unreacted mercaptan to form hydrogen chloride, which in turn, partially at least, can form water and the chloride by reacting with the resulting glycol. These reactions are represented by the following equations:

Sulfonium formation:



Elimination of hydrogen chloride:



These two types of decomposition manifest themselves readily in the distillation of the product. Above 1 mm. Hg pressure, the distillations are accompanied by large residues which are free of sulfhydryl groups, and in which the increasing sulfur and decreasing chlorine content approximate that obtained from a polythio ether of higher molecular weight. This indicates the removal of lower molecular weight volatile decomposition products which contain chlorine.

EXPERIMENTAL

Synthesis of 2-chloroethyl 2-hydroxy ethyl sulfide. a. *Runs at atmospheric pressure.* The apparatus used in this phase of the work consisted of a one-liter, three-necked Pyrex flask equipped with a mercury seal stirrer, thermometer, vinyl chloride inlet and outlet tubes, and a cold-finger type reflux condenser charged with a Dry Ice-acetone mixture. The flask was surrounded by a metal 4-liter bath into the side of which was installed a 6" x 6" Vycor window to allow the radiation from a CH₄ Hg-vapor lamp to impinge upon the reactants. Water at a temperature of 9 to 10° was circulated through the bath during a run. The flask was charged with 83.6 g. (1.05 moles) of ethanolmercaptan (obtained from the Carbide and Carbon Chemicals Corporation; purity 98.0% by iodimetric titration in absolute methanol) and 175.9 g. (2.25 moles) of benzene (Baker's C.P. grade). The entire system was swept out with dry nitrogen gas and gaseous vinyl chloride (E. I. duPont de Nemours & Co., cylinder grade) was passed into the reaction mixture under constant irradiation from the ultraviolet light. The amount of vinyl chloride absorbed was calculated from two dry-test gas meters which were inserted in the vinyl chloride inlet and outlet lines. In those runs where a catalyst was employed, the latter was added prior to the vinyl chloride passage. At the end of each run an aliquot sample was removed and titrated for unreacted mercaptan with iodine, using anhydrous methanol as solvent. The results of these runs are tabulated in Table I.

In Table II similar data are presented for the reaction of 1.05 moles of ethanolmercaptan in 4.94 moles of methanol as solvent in place of 2.25 moles of benzene.

In order to determine the effect of purity of ethanolmercaptan on the progress of the condensation, the crude mercaptan (purity 97.8% by iodimetric titration) was distilled in an all glass column and a fraction boiling at 44.5° at 6 mm. was collected. The purity of the distilled ethanolmercaptan was found to be 99.8%. As seen from Table III, this purified mercaptan gave better results than the undistilled material.

b. *Distillation of product* The products of all runs, conducted in methanol at atmospheric pressure, in which the conversions of ethanolmercaptan to semi-H were greater than 90%, were combined for the purpose of isolating the product by stripping off methanol and subsequent fractionation. These operations were performed in a simple Fenske-type column approximately two feet in length and $\frac{3}{4}$ -inch diameter, packed with $\frac{1}{8}$ -inch helices. The initial pressure was 180 mm. which was slowly reduced to 4 mm. The stripped residue was analyzed for sulfur, chlorine, and free sulphydryl groups

Anal. Calc'd for C₄H₉ClOS: Cl, 25.22; S, 22.81.

Found. Cl, 19.83; S, 21.43; free SH groups (calculated as ethanolmercaptan), 0.05.

The stripped material was fractionated in the same column at 0.5–0.75 mm. A constant boiling fraction was isolated at 87° · n_D^{20} 1.5205.

Anal. Calc'd for C₄H₈ClOS. Cl, 25.22; S, 22.81.

Found: Cl, 23.53; S, 21.63.

The kettle residue, which underwent visible decomposition, was also analyzed for chlorine and sulfur.

Anal. Found: Cl, 13.76; S, 26.08; free SH groups (calculated as ethanolmercaptan), nil.

c. *Runs in sealed tubes.* Pyrex tubes of approximately one-inch diameter and 60 ml. capacity were charged with 4.457 g. (0.057 mole) of ethanolmercaptan and 6.90 g. (0.11 mole) of freshly condensed vinyl chloride free of stabilizer and with a catalyst, if used. The tubes were cooled in a Dry Ice-acetone bath and sealed. They were suspended vertically on the periphery of a circular circulating water-bath. The tubes were consequently under water, as was the 100 Watt S-4 mercury vapor lamp at the center of the bath, at a distance of 11 cm. from each tube. By this radial distribution, an equal amount of radiant energy impinged upon each tube. After the desired exposure time, each tube was again chilled, opened, evacuated to constant weight at 50° and subjected to a residual mercaptan analysis. Table IV

contains the data obtained from ethanolmercaptan of 98.0% purity while in Table V reaction data obtained from the use of 99.8% pure ethanolmercaptan are presented.

d. *Preparation of amyl disulfide* ($C_5H_{11}S_2$). An aqueous solution consisting of 45.0 g. of potassium iodide, 34.1 g. of iodine, and 250 ml. of water was added slowly with stirring to 25.0 g. of amyl mercaptan until the iodine color persisted. The mercaptan used was obtained from Sharples Chemicals, Inc., and probably is a mixture of C_5 mercaptans. After the reaction was complete, the small excess of iodine was reduced with sodium thiosulfate solution. The oily upper layer was separated and extracted with diethyl ether. Before distilling, the ether extract was dried over activated silica gel. The fraction boiling at 105–107° at 2.5 mm. (or 74–75° at 1 mm.) was collected: n_D^{25} 1.4867.

Anal. Calc'd for $C_{10}H_{22}S_2$: S, 31.07. Found: S, 31.10.

SUMMARY

Two methods for the photosynthesis of 2-chloroethyl-2-hydroxyethyl sulfide from ethanolmercaptan and vinyl chloride are described. The effect of amyl disulfide as reaction accelerator, as well as the effect of the purity of ethanolmercaptan on the reaction, are presented.

The reaction mechanism is postulated to be of the free radical nature.

ARMY CHEMICAL CENTER, MARYLAND

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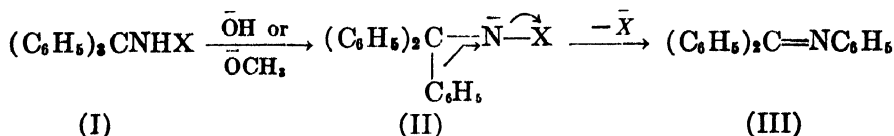
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REARRANGEMENT OF N-TRIPHENYLMETHYL-O-BENZYLHYDROXYLAMINE BY MEANS OF POTASSIUM AMIDE OR BORON TRIFLUORIDE

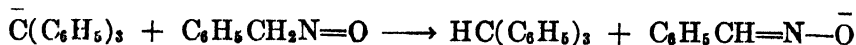
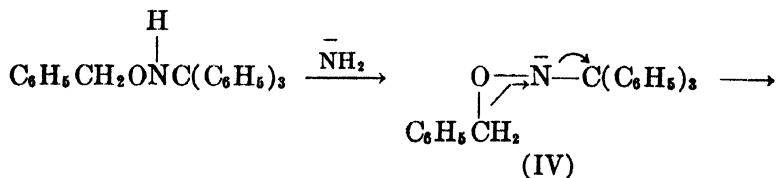
ERLE B. AYRES¹ AND CHARLES R. HAUSER

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The Stieglitz rearrangement of triphenylmethylaniline derivatives (I) to form benzophenone anil (III), involving α -elimination of HX and the shift of a phenyl group from carbon to nitrogen, has been effected by acidic reagents where X is alkoxy or hydroxy (1) and by basic reagents where X is halogen (2). With hydroxyl or methoxyl anion (II) is presumably formed as an intermediate, thus



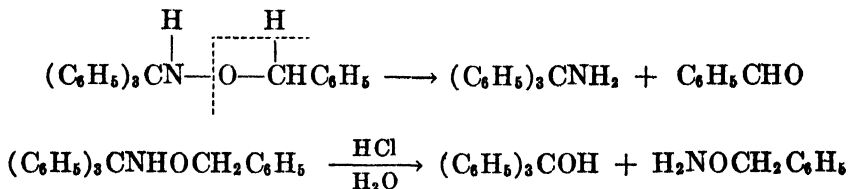
In the present investigation a study has been made of the decomposition of N-triphenylmethyl-O-benzylhydroxylamine (I, X = benzyloxy) in the presence of the amide ion, which should be a sufficiently strong base to produce a relatively high concentration of anion (II). However, aniline and benzophenone, the characteristic products of the Stieglitz rearrangement and subsequent hydrolysis, have been obtained in very low yields (generally less than 3%). With excess potassium amide in liquid ammonia and ether, the dark red color characteristic of the triphenylmethide ion soon develops, and from the reaction mixture there was obtained mainly triphenylmethane (60–65%) and benzaldoxime (25–37%). The latter was evidently not produced from benzaldehyde and hydroxylamine (or benzyloxyamine), which might conceivably have been formed in the reaction mixture, since blank experiments with these compounds, potassium amide, and triphenylmethane yielded no appreciable amount of the oxime under the conditions employed. Apparently the intermediate anion (IV) releases mainly the triphenylmethide ion concurrently with the shift of the benzyl group from oxygen to nitrogen to form α -nitrosotoluene, which is ionized to give the anion of benzaldoxime, thus



¹ Present address: Mellon Institute, Pittsburgh, Pa.

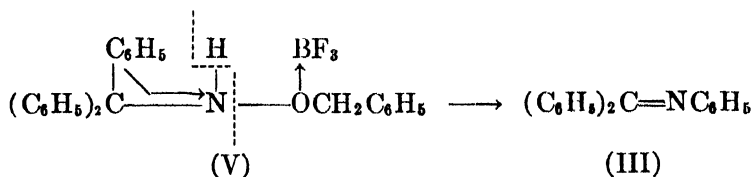
This reaction appears to be the first example of α -elimination of HX and rearrangement of a compound of the type RONHX ; in the present case, X is the triphenylmethyl group.

In addition to triphenylmethane, benzaldoxime, and the small amounts of aniline and benzophenone, there have been obtained from the reaction mixture of the benzyloxy derivative and potassium amide some triphenylmethanamine ($<4\%$), triphenylcarbinol, and benzoic acid (trace). As Guthmann and Stieglitz (1) have pointed out, the benzyloxy derivative might decompose to form triphenylmethanamine or triphenylcarbinol, thus



The first of these reactions could presumably be effected by potassium amide, but the second probably involved unreacted benzyloxy derivative and the hydrochloric acid used in the hydrolysis of benzophenone anil. The by-products, benzaldehyde and benzyloxyamine, have not been isolated; at least below 160° , the extent of the first of these reactions appears to be very small.

Guthmann and Stieglitz (1) realized the Stieglitz rearrangement of N-triphenylmethyl-O-benzylhydroxylamine (I, X = benzyloxy) in 40% yield with phosphorus pentoxide at 160° . We have effected this rearrangement at 60° (or less) with boron trifluoride, although the yield has been somewhat lower (29%). In contrast to basic reagents which remove the proton, these acidic reagents probably attack the benzyloxy group to form a coordination complex, for example, (V),² which undergoes the rearrangement, thus



It is significant that no benzaldoxime and not more than a trace of triphenylmethane, the products of the new rearrangement, could be isolated from the boron trifluoride reaction mixture. Since the triphenylmethyl carbon has no free pair of electrons, the acidic reagent, boron trifluoride, could not coordinate with it.

² It is recognized that boron trifluoride may coordinate at the nitrogen to a greater extent than at the oxygen; however, on the basis of modern theory, only the coordination at the oxygen should facilitate the Stieglitz rearrangement, which presumably involves the removal of the benzyloxy group with its bond pair of electrons. The yield (29%) of rearrangement product may be explained on the basis that either the coordination at the oxygen occurs to the extent of at least 29% or that this coordination takes place to a smaller extent but is in somewhat mobile equilibrium with that at the nitrogen.

EXPERIMENTAL

N-triphenylmethyl-*O*-benzylhydroxylamine. This substance (m.p. 118–119°) was prepared from triphenylmethyl chloride and *O*-benzylhydroxylamine as described by Guthmann and Stieglitz (1).

Reaction with potassium amide. The reaction of *N*-triphenylmethyl-*O*-benzylhydroxylamine with potassium amide has been carried out several times. Typical experiments are described below.

To a stirred solution of 0.028 mole of potassium amide in 125 ml. of liquid ammonia was added during five minutes a solution of 3.65 g. (0.01 mole) of *N*-triphenylmethyl-*O*-benzylhydroxylamine in 125 ml. of absolute ether. The mixture became dark red within five minutes. After three hours the ammonia was driven off, more ether being added to maintain constant volume, and the ether suspension refluxed for an hour or two. Wet ether and water were carefully added (the red color disappearing) and the mixture shaken. The aqueous (alkaline) phase, with which was combined a 5% sodium hydroxide extract of the ether phase, was saturated with carbon dioxide, and the oily *syn*-benzaldoxime³ (0.3 g, 25%), obtained after extraction with ether and evaporation of the solvent, was identified by conversion (3) to the *syn*-benzaldoxime benzoate (m.p. and mixed m.p. 101–102°). The ether phase, after three extractions with 3% hydrochloric acid (neutralization with aqueous ammonia yielding traces of triphenylmethanamine and of an unidentified oil), was distilled from the steam-bath, and the residue refluxed for ninety minutes with 10% hydrochloric acid. The mixture was diluted with water and shaken with ether. The aqueous acid phase was treated with bromine water, yielding a trace of tribromoaniline. The ether phase was divided into two equal portions and evaporated. The residue from one portion was refluxed in aqueous alcohol with hydroxylamine hydrochloride and sodium hydroxide, yielding a trace of benzophenone oxime (triphenylmethane mixed with triphenylcarbinol was mainly obtained). The residue from the other portion was dissolved in purified ligroin (b.p. 54–64°) and the solution extracted several times with cold concentrated sulfuric acid (the last extract was only slightly colored). After washing with water, the ligroin solution was dried and evaporated, yielding 0.9 g. of white solid, m.p. 81–87°. On dissolving in hot ethanol (0.1 g. of material m.p. 170–190° remained undissolved) and subsequent dilution with water, there was obtained 0.8 g. (65%) of triphenylmethane (m.p. and mixed m.p. 91–92°).

When *N*-triphenylmethyl-*O*-benzylhydroxylamine and potassium amide were allowed to react for 35 hours in liquid ammonia and ether (partly at room temperature), there were obtained yields of 37% of benzaldoxime, 61% of pure triphenylmethane, and 3% each of benzophenone oxime, tribromoaniline, and triphenylmethanamine.

When *N*-triphenylmethyl-*O*-benzylhydroxylamine (0.01 mole) and potassium amide (0.0115 mole) were refluxed in benzene for about two hours, there were obtained a 41% yield of crude benzaldoxime and a 57% yield of crude triphenylmethane, identified⁴ by carbonation of its potassium salt to form triphenylacetic acid (m.p. and mixed m.p. 262–263° uncor.).

Reaction with boron trifluoride. Boron trifluoride was passed over the surface of a stirred suspension of 3.65 g. (0.01 mole) of *N*-triphenylmethyl-*O*-benzylhydroxylamine in 75 ml. of ligroin (b.p. 74–90°) for thirty minutes at room temperature and then for ninety minutes longer as the temperature was gradually raised to 60°. The cooled mixture was stirred with 25 g. of sodium acetate in 80 ml. of water, the caked material on the sides of the flask being broken up. After being made alkaline with sodium hydroxide solution, the mixture

³ It is possible that this product was contaminated with the *anti*-isomer, since a mixture of the two isomers is produced on oxidation of benzyloxyamine to *bis*-nitrosotoluene and treatment with sodium ethoxide; [Behrend and König, *Ann.*, **263**, 214, 348 (1891)]. If formed, the *anti* benzaldoxime would probably have been partly decomposed by the potassium amide to benzonitrile or benzamidine [see Vermillion and Hauser, *J. Org. Chem.*, **6**, 507 (1941)], small amounts of which may have been overlooked.

⁴ We are indebted to Dr. Erwin Baumgarten for this identification.

was shaken vigorously and filtered. The solid was dissolved in ether and the solution extracted with sodium hydroxide. The combined aqueous alkaline solution was saturated with carbon dioxide, but no benzaldoxime could be isolated. The combined ligroin and ether solution was evaporated and the residue heated with 10% hydrochloric acid, diluted, and shaken with ether. The aqueous acid phase, on treatment with aqueous bromine, gave 0.962 g. (29%) of tribromoaniline (m.p. and mixed m.p. 119-120°). The ether phase, on evaporation, yielded benzophenone, which was converted to its oxime (27%, m.p. and mixed m.p. 143-144°). A search for triphenylmethane yielded only a trace of what might have been this substance, melting at 87-90°.

SUMMARY

1. In the presence of potassium amide, N-triphenylmethyl-O-benzylhydroxylamine undergoes the Stieglitz rearrangement (to benzophenone anil) to only a small extent; instead, the main reaction involves elimination of triphenylmethane accompanied by rearrangement of the benzyl group from oxygen to nitrogen to form benzaldoxime.

2. The Stieglitz rearrangement is realized in the presence of boron trifluoride.

3. Mechanisms are considered.

DURHAM, NORTH CAROLINA

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ALKYLATION OF PHENOL WITH *t*-BUTYL ALCOHOL IN THE PRESENCE OF PERCHLORIC ACID

CARLTON A. SEARS, JR.¹

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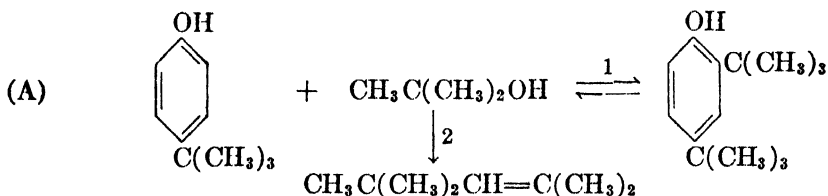
The alkylation of phenol has been realized by the use of *t*-butyl alcohol or isobutylene in the presence of such catalysts as aluminum chloride, zinc chloride mixed with small amounts of aluminum chloride, phosphoric, and sulfuric acids (1, 2, 3, 4, 5, 6).

Perchloric acid has a very high hydrogen ion activity (7) and the fact that it retains this activity in the presence of organic compounds (8) should make it an effective catalyst in some organic reactions. The lack of investigation in this field is probably due to the hazardous nature of perchloric acid-organic mixtures (9).

With these facts in mind the effect of perchloric acid catalysis in alkylation of phenol with *t*-butyl alcohol was investigated, first on very small amounts of the reactants (50 mg.). The quantities of the reactants were successively increased until the amounts presented in the experimental data were reached. Such precautions should always be observed when using perchloric acid with organic materials.

Relatively good yields of 2,4-di-*t*-butylphenol (see Table I) are obtained in the presence of perchloric acid, whereas by other means of catalysis the main product is the 4-*t*-butylphenol.

Apparently the reaction is in equilibrium (A); 1 being a fast reaction, 2 being slow.



The di-substituted product is less soluble in perchloric acid than the mono product. Therefore, the shift in equilibrium, which may occur only at the point of contact of the di-*t*-butylphenol and perchloric acid phases, is very slow.

In the ten-minute runs small amounts of the mono product and di-isobutylene were obtained. In the sixty-minute runs proportionately greater amounts of the mono product and di-isobutylene were obtained and in the twenty-hour run 4-*t*-butylphenol was isolated by merely extracting the organic layer and distilling off the di-isobutylene.

Acknowledgement. The author wishes to express sincerest thanks to Dr. Frederick R. Duke who suggested this problem, and whose advice and encouragement throughout the investigation made this paper possible.

¹ Present address: Severance Chemical Laboratory, Oberlin College, Oberlin, Ohio.

EXPERIMENTAL

Runs were made in 1:1, 1:2, and 1:3 molar ratios; the quantity of phenol was kept constant while that of the *t*-butyl alcohol was varied. Two complete runs were made under the same conditions and with the same treatment of the products. The time intervals were for ten minutes and sixty minutes. A third run was also made with the 1:3 molal ratio for a period of twenty hours.

I. *The reaction of phenol with t-butyl alcohol in the presence of perchloric acid.* To a stirred solution (the sixty-minute and twenty-hour runs were put on a mechanical shaker) of 24 g. (0.25 mole) of phenol, 30 cc. of water, and 100 cc. of 70% perchloric acid, 15 cc. (0.25 mole) of *t*-butyl alcohol was slowly added. The temperature was carefully observed and did not rise above 60° in any case. At the end of the time interval the mixture was transferred to a separatory funnel and the aqueous layer extracted three times with petroleum ether (60–70°). The combined ethereal solutions were then washed with water and separated. The organic layer was washed twice with a saturated solution of potassium bicarbonate² and, finally, again washed with water.

II. *4-t-Butylphenol.* The ethereal solution (I) from above was extracted with four different portions of a 10% potassium hydroxide solution. The combined extracts were acidi-

TABLE I
YIELD OF PRODUCTS, %

	MONO			DI		
	1:1	1:2	1:3	1:1	1:2	1:3
10 min. runs	5	10	16	5	21	44
60 min. runs	26	32	21	5	27	28
20 hr. run	—	—	48			

fied with hydrochloric acid and the mixture transferred to a separatory funnel. The aqueous layer was extracted two times with petroleum ether. 4-*t*-Butyl phenol was obtained from the ether solution. The impure product was recrystallized from ligroin, white needles, m.p. 99°.

Anal. Calc'd for $C_{10}H_{14}O$: C, 80.00; H, 9.33.

Found: C, 80.02; H, 9.24.

2,4-Di-t-butylphenol. The original ethereal solution (I) was next extracted with four different portions of Claisen solution (10). The combined extracts were treated the same as the 10% potassium hydroxide extracts. 2,4-Di-*t*-butylphenol was obtained from this fraction. The impure product was purified with ligroin, white crystals, m.p. 54°.

Anal. Calc'd for $C_{14}H_{22}O$: C, 81.55; H, 10.63.

Found: C, 81.34; H, 10.01.

The twenty-hour run was made the same as above, up to II. At this point the solution was transferred to a distilling flask, the ether and di-isobutylene (b.p. 101–102°, n_D 1.415, readily adds bromine) were distilled off and the 4-*t*-butyl phenol crystallized on cooling. The impure product was recrystallized from ligroin; m.p. 99°.

Anal. Calc'd for $C_{10}H_{14}O$: C, 80.00; H, 9.33.

Found: C, 80.10; H, 9.54.

4-t-Butylphenyl benzoate. Two 5-cc. portions of benzoyl chloride were added slowly, with vigorous shaking, to 0.5 g. of 4-*t*-butylphenol dissolved in 10 cc. of anhydrous pyridine. The solution was set aside for five hours then poured into cold water. The water mixture

² The potassium salt of perchloric acid is very insoluble in organic materials, whereas the sodium salt is appreciably soluble.

was extracted with ether and the ethereal solution was separated and evaporated. The benzoate which remained was recrystallized from alcohol, m.p. 83°.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.03; H, 7.08.

Found: C, 80.00; H, 7.01.

*2,4-Di-*t*-butylphenyl benzoate.* The benzoate of the di-substituted product was obtained by the procedure given above, m.p. 98°.

Anal. Calc'd for $C_{21}H_{26}O_2$: C, 81.29; H, 8.38.

Found: C, 81.21; H, 8.27.

SUMMARY

Perchloric acid is presented as an effective and rapid catalyst for the alkylation of phenol with *t*-butyl alcohol.

A method to obtain relatively good yields of 2,4-di-*t*-butylphenol is presented.

EAST LANSING, MICH.

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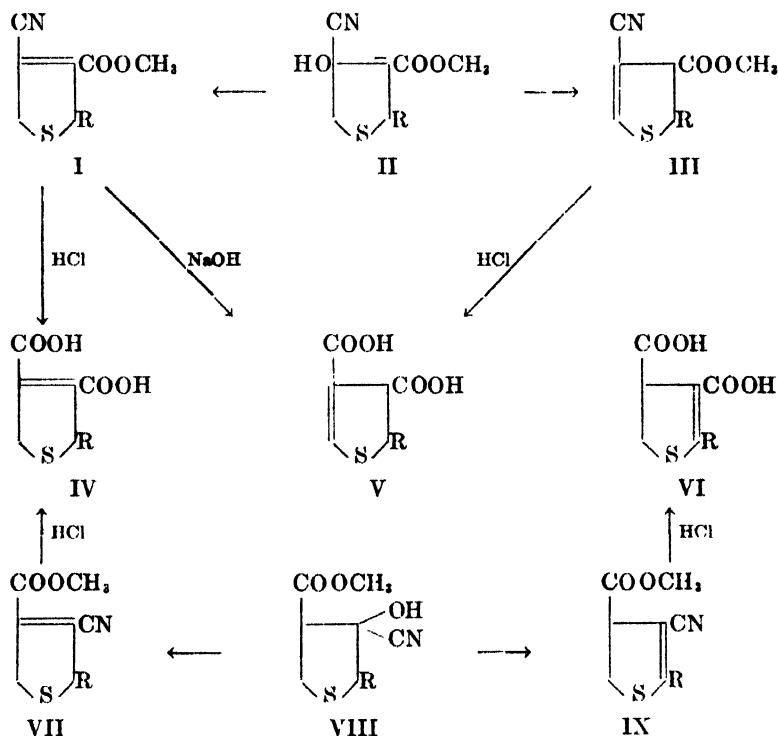
BIOTIN. XI. THE STRUCTURE OF 2-ALKYLDIHYDROTHIOPHENE-3,4-DICARBOXYLIC ACIDS

B. R. BAKER, MERLE V. QUERRY, AND ARTHUR F. KADISH

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In some previous communications of this series (1, 2, 3), it was shown that dehydration and acid hydrolysis of cyanohydrin esters of types II and VIII gave 2-alkyldihydrothiophene-3,4-dicarboxylic acids in which the position of the double bond was unknown. The double bond has now been established to be in the 3,4-position.

3-Carbomethoxy-4-ketothiophane (4), on treatment with hydrogen cyanide, gave a cyanohydrin, II ($R = H$), which was dehydrated with phosphorus oxychloride and pyridine in benzene to a crystalline 3-carbomethoxy-4-cyanodihydrothiophene (I or III, $R = H$) in 70% yield. Acid hydrolysis of the cyano ester gave a dihydrothiophene-3,4-dicarboxylic acid, A, m.p. 183–184°, whereas



alkaline hydrolysis gave an isomeric dihydrothiophene-3,4-dicarboxylic acid, B, m.p. 180–181° dec. An investigation showed that the absorption spectra (Figure 1) of the cyano ester and the diacid, A, were similar, but that of the diacid, B, was radically different, indicating that a shift of the double bond had taken place during the alkaline hydrolysis. Although the diacid, A, was readily

reduced with sodium amalgam to a mixture of the *cis* and *trans* isomers of thiophane-3,4-dicarboxylic acid, the diacid, B, was unaffected under the same conditions. However, the latter could be reduced to *trans*-thiophane-3,4-dicarboxylic acid¹ by increasing the temperature, time of reaction and quantity of sodium amalgam, thus demonstrating that the diacid, B, was truly a dihydrothiophene-3,4-dicarboxylic acid.

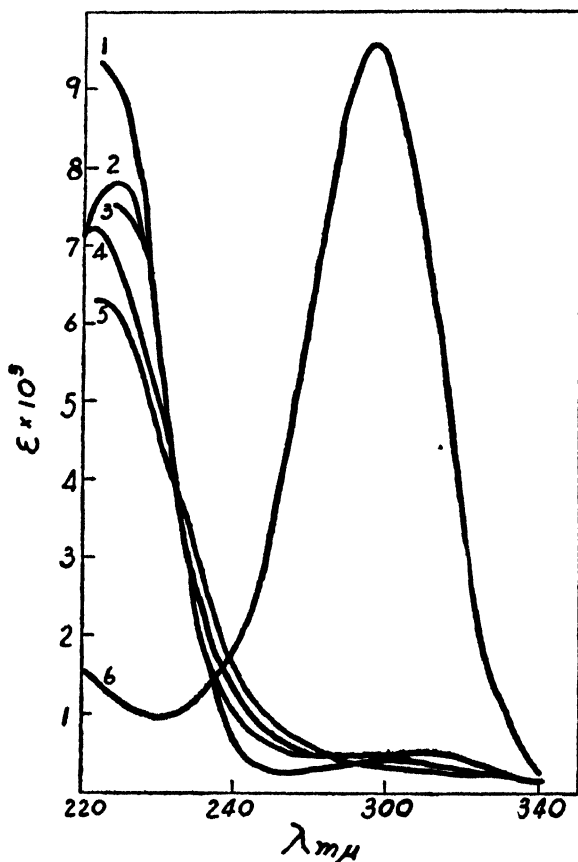


FIG. 1. 1: Diacid "A"; 2: I, R = H; 3: VII, R = $-\text{CH}_2\text{COOH}$; 4: IV, R = $-(\text{CH}_2)_4\text{COOH}$; 5: IV, R = $-\text{CH}_2\text{COOH}$; 6: Diacid "B". Absorption curves determined in water.

Some similar observations have been made on the cyclohexene-1,2-dicarboxylic acids by Baeyer (5). The $\Delta^{1,2}$ isomer was readily reduced with sodium amalgam to cyclohexane-1,2-dicarboxylic acid, whereas the $\Delta^{2,3}$ isomer could not be reduced under the same conditions. Furthermore, the $\Delta^{1,2}$ isomer was rearranged to the $\Delta^{2,3}$ isomer under the influence of hot strong alkali. The same type of result has been observed with the cyclopentene-1,2-dicarboxylic acids (6).

¹ The surprising observation that only the *trans* isomer was formed in this reaction was readily understood when it was found that the pure *cis* isomer could be rearranged to *trans* under the stringent alkaline conditions necessary for the reduction.

In both ring systems the positions of the double bonds were proven beyond doubt. If an analogy can be carried to the dihydrothiophene-3,4-dicarboxylic acids, then the diacid, A, should have the structure IV ($R = H$) and the diacid, B, that of V ($R = H$).

A comparison of the absorption spectra of the diacids, A and B, with that of maleic acid (Figure 2) indicated that A had the $\text{HOOC}-\text{C}=\text{C}-\text{COOH}$ linkage, as both A and maleic acid absorbed strongly in the 215–225 $m\mu$ region, but only weakly in 275–305 $m\mu$ region. In contrast, β -ethylthiocrotonic acid (7), 2-

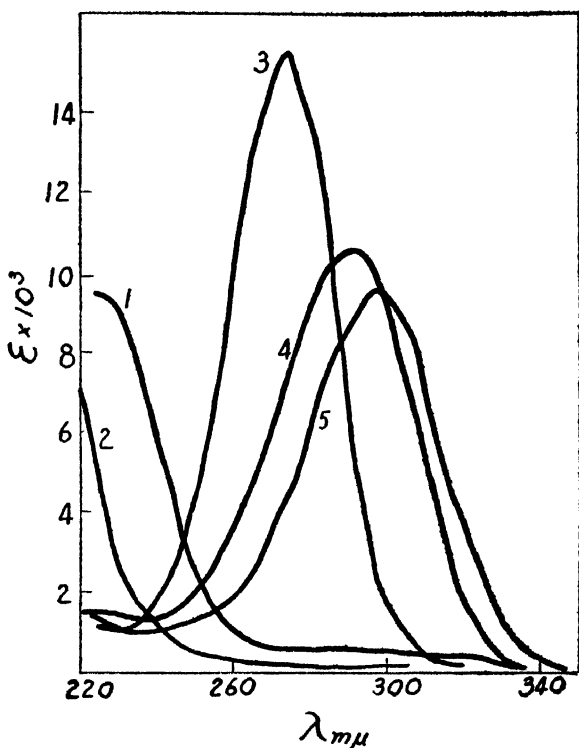
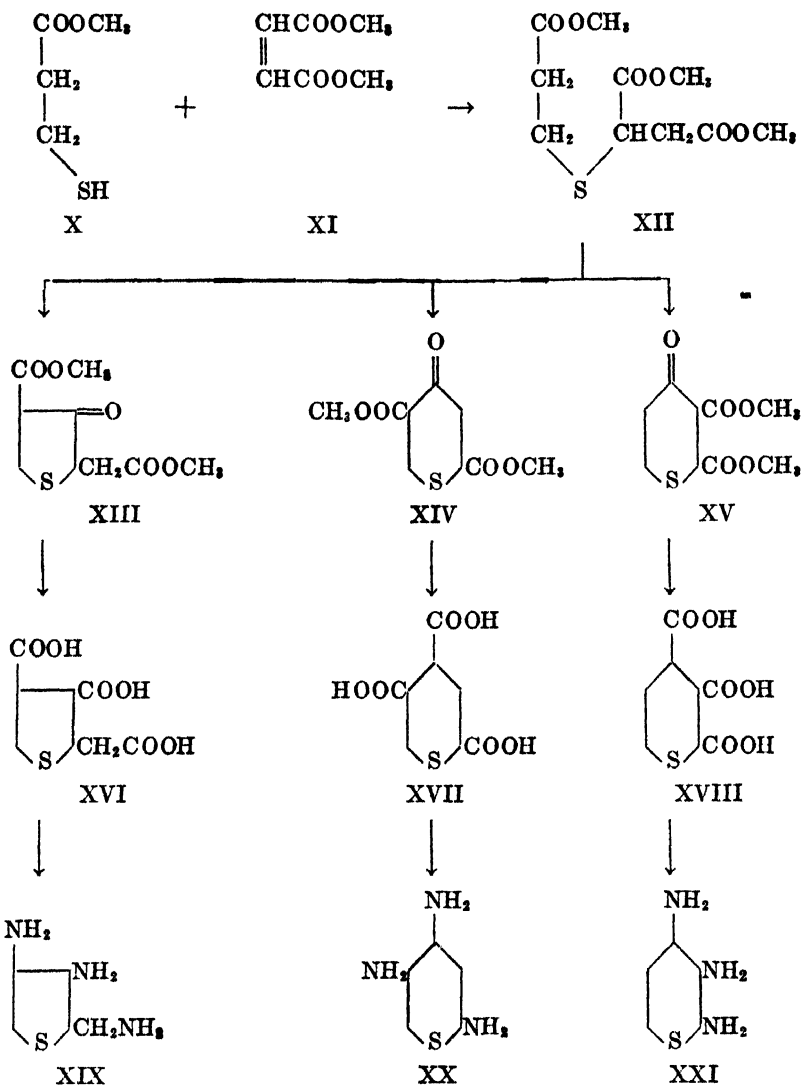


FIG. 2. 1: Diacid "A"; 2: maleic acid (12); 3: β -ethylthiocrotonic acid; 4: 2-propyl-4-*n*-butylthio-2,5-dihydrothiophene-3-carboxylic acid; 5: Diacid "B".

propyl-4-butylthio-2,5-dihydrothiophene-3-carboxylic acid and the diacid, B, each had a maximum in the 275–305 $m\mu$ region, but only low absorption in the 220–230 $m\mu$ region, indicating that the diacid, B, had the $-\text{S}-\text{C}=\text{C}-\text{COOH}$ linkage. Thus, the absorption spectra also indicate that the diacid, A, has structure IV ($R = H$) and the diacid, B, that of V ($R = H$).

That the above suppositions were correct was verified by chemical proof. Dehydration and acid hydrolysis of the isomeric cyanohydrin esters, II and VIII, should give isomeric unsaturated diacids, V and VI, respectively if dehydration has taken place towards the sulfur atom. However, if dehydration forms a

double bond in the 3,4 position, then the identical diacid, IV, should be obtained from both cyanohydrins. This was tested with $R = -CH_2COOCH_3$. The products obtained in both cases were indeed identical, proving that the double bond was in the 3,4 position.



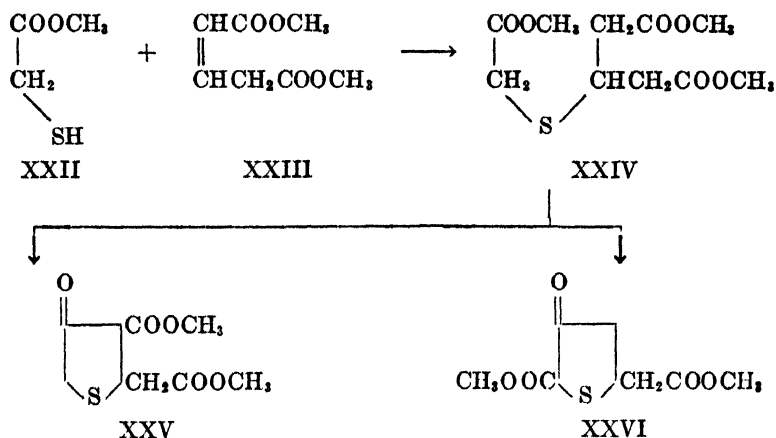
Methyl β-mercapto-3-oxopropionate (X) condensed smoothly with methyl maleate in the presence of piperidine. The resultant thiotriester, XII, was cyclized by the Dieckmann method to 2-carbomethoxymethyl-3-keto-4-carbomethoxythiophane (XIII). The latter, converted to the cyanohydrin, VIII ($R = -CH_2COOCH_3$), was dehydrated with phosphorus oxychloride and pyridine in benzene to the crystalline 2-carbomethoxymethyl-3-cyano-4-carbomethoxy-2,5-dihydrothiophene (VII, $R = -CH_2COOCH_3$). Acid hydrolysis resulted in

2-carboxymethyl-2,5-dihydrothiophene-3,4-dicarboxylic acid (IV, $R = -CH_2COOH$), m.p. 211–213°dec.

The Dieckmann cyclization of XII can theoretically take place to give the thiophane, XIII, and/or the penthianes, XIV and XV. That the cyclization formed the thiophane keto ester, XIII, was proved as follows:²

2-Carboxymethyl-2,5-dihydrothiophene-3,4-dicarboxylic acid (IV, $R = -CH_2COOH$) was reduced with sodium amalgam to the thiophane tricarboxylic acid, XVI, m.p. 191°. This acid was degraded, *via* the trihydrazide and the triurethan, to the stable triamine, XIX, identified as its trihydrobromide, tripicrate, and triuramido derivatives. If the Dieckmann cyclization had formed either of the penthiane keto esters, XIV or XV, then the above sequence of reactions would have resulted in the hydrolytically unstable triamines, XX and XXI, respectively. A molecule in which thio and amine groups are attached to the same carbon atom has been shown by Brown and Kilmer (9) to be unstable, as this linkage is cleaved on hydrolysis of the urethan derivative, with the formation of ammonia.

Methyl glutaconate (XXIII) readily added methyl thioglycolate (XXII) with formation of the thiotriester, XXIV. Dieckmann cyclization of the latter in hot toluene proceeded in 60% yield to the keto esters, XXV and XXVI. Ferric chloride titration (4) indicated that the product contained 87% of the desired keto ester, XXV. This was converted to 2-carboxymethyl-2,5-dihydrothiophene-3,4-dicarboxylic acid (IV, $R = -CH_2COOH$) *via* the intermediates II and I ($R = -CH_2COOCH_3$). The product melted at 211–213°dec. and gave no depression in m.p. when mixed with the triacid obtained from the isomeric cyanohydrin, VIII ($R = -CH_2COOCH_3$).

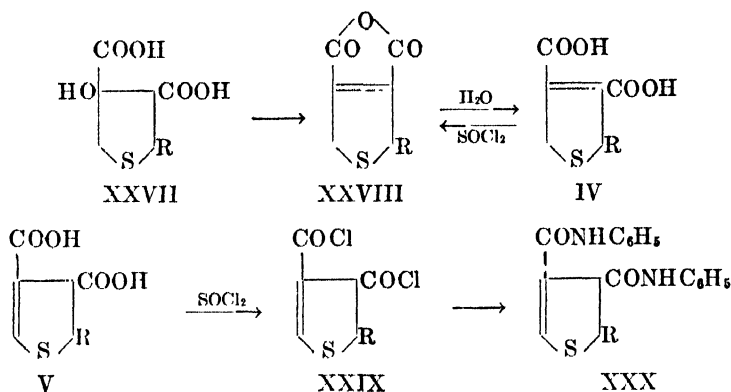


The absorption spectra (Fig. 1) of the cyano esters, VII ($R = -CH_2COOCH_3$, $-(CH_2)_4COOCH_3$ and H), the triacids, IV ($R = -CH_2COOH$ or $-(CH_2)_4COOH$), and the dihydrothiophene-3,4-dicarboxylic acid, A, were almost identi-

² There was a good probability that the reaction would give a thiophane rather than a penthiane ring as methyl β,β' -thiodipropionate does not cyclize appreciably with the conditions used.

cal, showing that in all these molecules the double bond was in the 3,4 position.³

A reagent which could be used to distinguish between a 2,5-dihydrothiophene-3,4-dicarboxylic acid (IV) and its 2,3-dihydro isomer was thionyl chloride. With the model compounds ($R = H$), IV formed an anhydride (XXVIII) whereas V ($R = H$), formed a diacid chloride characterized as its dianilide, XXX ($R = H$).⁴



Treatment of 3-hydroxythiophene-3,4-dicarboxylic acid (XXVII, $R = H$) with acetic anhydride gave a mixture of 2,5-dihydrothiophene-3,4-dicarboxylic anhydride (XXVIII, $R = H$) and 3-acetoxythiophene-3,4-dicarboxylic anhydride. As this dehydration took place to give a double bond in the 3,4-position, it is probable that the similar dehydration of 2-(γ -phenoxypropyl)-3-hydroxythiophene-3,4-dicarboxylic acid and XXVII ($R = C_6H_5O(CH_2)_3-$) also took place (8) to give the same diacid with a double bond in the 3,4 position.

Acknowledgment. The authors wish to thank Dr. Y. SubbaRow for his helpful suggestions. They are also indebted to Dr. E. I. R. Stokstad for the absorption spectra and Mr. Louis Brancone and his staff for the microanalyses.

EXPERIMENTAL

3-Cyano-4-carbomethoxy-2,5-dihydrothiophene (I, $R = H$). To 80 cc. of liquid hydrogen cyanide and 0.5 cc. of 50% potassium hydroxide cooled in an ice-bath was added in portions a solution of 148 g. of 3-keto-4-carbomethoxythiophene (4) in 50 cc. of methanol, maintaining the temperature at 10–20°. After fifteen hours at 0–5°, the mixture was acidified with 3 cc. of 85% phosphoric acid and evaporated to dryness *in vacuo*; yield of crude cyanohydrin (II, $R = H$), 178 g.

Dehydration of 107 g. of the crude cyanohydrin in the same way as described for the corresponding ethyl ester (1) resulted in 75 g. (82%) of product, b.p. 120–125° (1 mm.), m.p. 44–50°. Recrystallization from heptane-benzene gave 65 g. (70%) of white crystals, m.p. 55–57°.

Anal. Calc'd for $C_7H_7NO_2S$: C, 49.7; H, 4.2; N, 8.3.

Found: C, 49.9; H, 4.3; N, 8.5.

³ The structures postulated by Surrey, Hammer, and Suter (10) for a similar series of compounds with $R = \text{phenyl}$ do not agree with these results.

⁴ Similarly, Baeyer (5) observed that Δ^1 -tetrahydrophthalic acid formed an anhydride much more easily than did the isomeric Δ^2 -tetrahydrophthalic acid.

2,5-Dihydrothiophene-3,4-dicarboxylic acid (IV, $R = H$). A mixture of 5 g. of I ($R = H$), 15 cc. of acetic acid, and 25 cc. of concentrated hydrochloric acid was refluxed for sixteen hours, then evaporated to dryness *in vacuo*. The residue was extracted with hot acetone, filtered from ammonium chloride, and again evaporated to give 4.9 g. of solid, m.p. 163–170°. Recrystallization from acetone-benzene resulted in 4 g. (77%) of white crystals, m.p. 183–184°.

Anal. Calc'd for $C_6H_4O_4S$: C, 41.3; H, 3.5.

Found: C, 41.4; H, 4.0.

Reduction with sodium amalgam in dilute alkali at 70–80° as previously described (1) gave a nearly quantitative yield of a mixture of the *cis* and *trans* isomers of thiophane-3,4-dicarboxylic acid.

4,5-Dihydrothiophene-3,4-dicarboxylic acid (V, $R = H$). A solution of 5 g. of I ($R = H$) in 25 cc. of alcohol was refluxed with 10 g. of sodium hydroxide in 25 cc. of water for sixteen hours. The solution was acidified, clarified by filtration, and extracted three times with ethyl acetate. Dried with magnesium sulfate, the extracts were evaporated to dryness *in vacuo*. The residual solid (5 g., m.p. 165–172°) was recrystallized from acetone-benzene, white crystals, m.p. 180–181° dec.; yield, 3.3 g. (64%). A mixture with 2,5-dihydrothiophene-3,4-dicarboxylic acid (IV, $R = H$) (isomer A) melted below 150°.

Anal. Calc'd for $C_6H_4O_4S$: C, 41.3; H, 3.5.

Found: C, 41.5; H, 3.8.

Reduction of 4,5-dihydrothiophene-3,4-dicarboxylic acid (V, $R = H$). Attempted reduction of this compound (isomer B) with sodium amalgam in dilute alkali at 70–80° as previously described (1) resulted in recovery of 94% of somewhat impure starting material, m.p. 165–168° dec., identified by mixed m.p.

A solution of 3.3 g. of isomer B in 60 cc. of 1 *N* sodium hydroxide was stirred with 125 g. of 2% sodium amalgam on the steam-bath for four hours. The reaction mixture was worked up as usual (1); yield after recrystallization from benzene, 2.1 g. (64%), m.p. 124–125°, resolidifies and remelts at 134–135°. A mixture with an authentic sample of *trans*-thiophane-3,4-dicarboxylic acid (1) gave no depression in the m.p. By retreatment of the filtrate with sodium amalgam as just described, an additional 0.40 g. (12%) of *trans* diacid was obtained with the same m.p.

When pure *cis*-thiophane-3,4-dicarboxylic acid (1) was heated with 20% alkali on the steam-bath for four hours, 60% of *trans*-thiophane-3,4-dicarboxylic acid was obtained, m.p. and mixed m.p. 135–136°.

2-Propyl-3-carbomethoxy-4,4-dibutylthiophane. A mixture of 50 g. of 2-propyl-3-carbomethoxy-4-ketothiophane (8) and 50 cc. of *n*-butyl mercaptan was treated with hydrogen chloride gas until turbid (about five minutes). After twenty-two hours, during which a layer of water separated, the oil was dissolved in benzene and washed twice each with 10% sodium hydroxide and water. Distillation gave 50 g. (55%) of product, b.p. 158–162° (1 mm.), n_D^{20} 1.5373.

Anal. Calc'd for $C_{17}H_{32}O_2S_2$: C, 56.1; H, 8.9.

Found: C, 56.6; H, 8.8.

2-Propyl-4-n-butylthio-2,5-dihydrothiophene-3-carboxylic acid. A solution of 5.6 g. of the above mercaptan in 25 cc. of alcohol and 6 g. of potassium hydroxide in 6 cc. of water was refluxed for sixteen hours, diluted with water, acidified, and extracted with benzene. The benzene layer was extracted with 5% sodium hydroxide and water. The latter two were combined and acidified. The oil was extracted with benzene. The residue on evaporation was recrystallized from dilute alcohol, then benzene-petroleum ether, white crystals, m.p. 137–137.5°.

Anal. Calc'd for $C_{15}H_{20}O_4S_2$: C, 55.3; H, 7.7.

Found: C, 55.6; H, 7.4.

The yield was poor, and most of the starting material could be recovered.

Methyl β -carbomethoxy- β,β' -thiodipropionate (XII). To a mixture of 580 g. of methyl

β -mercaptopropionate (8) and 5 cc. of piperidine was added dropwise with stirring and ice-cooling. 640 cc. of methyl maleate, at such a rate that the temperature was 35–40° (twenty minutes). The solution was allowed to stand for one hour, and was distilled. After a fore-run of methyl fumarate, the product was obtained as a colorless oil, b.p. 155–165° (1 mm.); yield, 1244 g. (98%). The b.p. varies considerably with bath temperature.

Anal. Calc'd for $C_{10}H_{16}O_6S$: C, 45.5; H, 6.1.

Found: C, 46.0; H, 6.1.

2-Carbomethoxymethyl-3-keto-4-carbomethoxythiophane (XIII). To a solution of 100 g. of XII in 300 cc. of toluene and 35 cc. of methanol was added 25 g. of commercial sodium methoxide. The mixture was refluxed for two hours. The sodium methoxide dissolved soon after the b.p. was reached. Cooled to 5°, the reaction mixture was diluted with ice and water. The separated aqueous layer was immediately run into iced hydrochloric acid and the toluene extracted once more with ice-water. The oily keto ester was extracted with toluene, the extract was washed with aqueous sodium bicarbonate and water. Distillation gave 46 g. (52%) of a colorless oil, b.p. 135–155° (1 mm.), mainly at 145°. The product, which was suitable for the next step, solidified on standing. Several recrystallizations from benzene-petroleum ether gave white crystals, m.p. 71–74°.

Anal. Calc'd for $C_9H_{12}O_6S$: C, 46.6; H, 5.2.

Found: C, 46.4; H, 5.5.

In larger runs the yield was 35–45%. Without the methanol, the sodium methoxide became coated and the yield was poor.

2 - Carbomethoxymethyl - 3 - cyano - 4 - carbomethoxy - 2,5 - dihydrothiophene (VII, R = -CH₂COOCH₃). To 121 g. of molten XIII super-cooled to 20° was added quickly 40 cc. of hydrogen cyanide and 0.5 cc. of 50% potassium hydroxide. The mixture rapidly became homogeneous on swirling in an ice-bath. After fifteen hours at 0°, the mixture was acidified with 3 cc. of 85% phosphoric acid and volatile material was removed *in vacuo* on the steam-bath. The crude cyanohydrin, VIII (R = -CH₂COOCH₃) was dehydrated with 100 cc. of phosphorus oxychloride and 390 cc. of pyridine in 390 cc. of benzene in the same manner as described for I (R = H) except that the reaction was allowed to proceed for four hours. Distillation gave 90.4 g. (68%) of product, b.p. 155–165° (1 mm.), which solidified in the receiver. Recrystallization from benzene-heptane resulted in light yellow crystals, m.p. 88–89.5°.

Anal. Calc'd for $C_{10}H_{11}NO_4S$: C, 49.8; H, 4.6; N, 5.8.

Found: C, 49.4; H, 4.7; N, 6.1.

2-Carboxymethyl-2,5-dihydrothiophene-3,4-dicarboxylic acid (IV, R = -CH₂COOH). A mixture of 41.2 g. of recrystallized VII (R = -CH₂COOCH₃), 90 cc. of acetic acid, and 200 cc. of concentrated hydrochloric acid was refluxed for sixteen hours, then worked up as described for VII (R = H); yield of white crystals, 22.3 g. (56%), m.p. 211–213° dec.

Anal. Calc'd for $C_8H_8O_6S$: C, 41.3; H, 3.5.

Found: C, 41.7; H, 3.4.

2-Carboxymethylthiophane-3,4-trans-dicarboxylic acid (XVI) A solution of 25 g. of IV (R = -CH₂COOH) in 250 cc. of 5% sodium hydroxide was stirred with 400 g. of 2% sodium amalgam on the steam-bath for three hours. After the addition of 14 g. of sodium hydroxide, the mixture was heated on the steam-bath for fifteen hours. The solution was decanted from the mercury, acidified, saturated with salt and extracted with four 125-cc. portions of ethyl acetate. The combined extracts, dried with magnesium sulfate and Norited, were concentrated *in vacuo* until the product began to crystallize, then diluted with one volume of benzene; yield, 11.7 g. (47%), m.p. 183–185°. Recrystallization from acetone-ethyl acetate gave white crystals, m.p. 191–191.5°. Analytical values obtained for carbon and hydrogen on this molecule were quite variable.

The methyl ester was prepared in 80% yield by the continuous drying method (8) using methanol, chloroform, and sulfuric acid; b.p. 160–165° (1 mm.). Recrystallization from methanol gave white crystals, m.p. 47°.

Anal. Calc'd for $C_{11}H_{16}O_6S$: C, 47.8; H, 5.8.

Found: C, 48.3; H, 6.0.

2-Carboxyhydrazidomethylthiophane-3,4-trans-dicarboxyhydrazide. A mixture of 2.7 g. of 2-carbomethoxymethyl-3,4-trans-dicarbomethoxythiophane and 5.4 cc. of 100% hydrazine hydrate was heated on the steam-bath with shaking. In three minutes a crystal paste had formed. After being heated fifteen minutes more, the mixture was triturated with methanol; yield, 2.5 g. (93%), m.p. 241° dec. Recrystallization from water-methanol gave white crystals of unchanged m.p.

Anal. Calc'd for $C_8H_{16}N_6O_6S$: C, 34.8; H, 5.8; N, 30.5.

Found: C, 34.5; H, 6.1; N, 30.2.

2-Carbethoxymethyl-3,4-trans-dicarbethoxyminothiophane. To a solution of 2.3 g. of the above trihydrazide in 100 cc. of 1 N hydrochloric acid and 50 cc. of chloroform was added dropwise with stirring and ice-cooling a solution of 2.0 g. of sodium nitrite in 50 cc. of water over a period of twenty-five minutes. After being stirred ten minutes more, the mixture was separated and the aqueous layer extracted once more with chloroform. The combined chloroform extracts, dried with calcium chloride at 0° , were diluted with 50 cc. of absolute ethanol and refluxed for one hour. After removal of the solvent, the residue was recrystallized from dilute alcohol; yield, 1.2 g. (40%), m.p. $201-204^\circ$.

Anal. Calc'd for $C_{14}H_{26}N_2O_6S$: C, 46.3; H, 7.0; N, 11.7.

Found: C, 46.7; H, 7.3; N, 11.8.

2-Aminomethyl-3,4-trans-diaminothiophane (XIX) trihydrobromide A mixture of 300 mg of the above triurethan and 6 cc. of 48% hydrobromic acid was refluxed twenty-five minutes. The solution was cooled in an ice-bath, the product was collected on a glass filter and washed with acetone. After drying at 100° , the yield was 255 mg. (79%), of crystals which sintered at $170-200^\circ$ and decomposed at 293° . Recrystallization from 48% hydrobromic acid gave white needles which partially melted with gas evolution at 170° , resolidified and remelted at 302° dec.

Anal. Calc'd for $C_8H_{16}Br_3N_2S \cdot 2H_2O$: C, 14.1; H, 4.7; N, 9.9.

Found: C, 14.4; H, 5.4; N, 10.0.

The tripicrate formed orange-yellow crystals from dilute methanol, m.p. 224° dec.

Anal. Calc'd for $C_{23}H_{22}N_{12}O_{21}S$: N, 20.1. Found: N, 20.0.

The trihydrobromide gave a triuramido derivative with potassium cyanate in 85% yield: white crystals from water, m.p. 282° dec.

Anal. Calc'd for $C_8H_{16}N_6O_3S$: C, 34.8; H, 5.8; N, 30.5.

Found: C, 34.8; H, 5.9; N, 30.2.

Methyl β -(carbomethoxymethylthio)glutarate (XXIV). To a mixture of 58 g. of methyl thioglycolate and 82.5 g. of methyl glutaconate (II) was added 0.6 cc. of piperidine. The temperature was kept below 50° by ice-cooling. After standing for sixteen hours, the mixture was dissolved in chloroform, washed with water and distilled: colorless oil, b.p. $155-163^\circ$ (1 mm.); yield, 83.6 g. (60%).

Anal. Calc'd for $C_{10}H_{16}O_6S$: C, 45.5; H, 6.1.

Found: C, 45.1; H, 6.1.

2-Carbomethoxymethyl-3-carbomethoxy-4-ketothiophane (XXV). From 40 g. of XXIV, 13.5 cc. of methanol, 120 cc. of toluene, and 10 g. of sodium methoxide was obtained, after refluxing for one hour, 21 g. (60%) of colorless oil, b.p. $137-143^\circ$ (1 mm.), according to the procedure described for the isomeric keto ester (XIII). Ferric chloride titration (4) indicated that the keto ester was 87% pure, containing 13% of the isomeric XXVI.

Anal. Calc'd for $C_9H_{12}O_6S$: C, 46.6; H, 5.2.

Found: C, 46.8; H, 5.3.

The semicarbazone formed white crystals from dilute methanol, m.p. $159-164^\circ$.

Anal. Calc'd for $C_{10}H_{15}N_3O_6S$: C, 41.7; H, 5.1; N, 14.5.

Found: C, 41.9; H, 5.6; N, 14.5.

2 - Carbomethoxymethyl - 3 - carbomethoxy - 4 - cyano - 2,5 - dihydrothiophene (I, R =

— $\text{CH}_2\text{COOCH}_3$). This compound was prepared in 77% yield in the same manner as described for the isomeric cyano ester (VII, $\text{R} = -\text{CH}_2\text{COOCH}_3$); yellow oil, b.p. 145–158° (1 mm.). A center cut at 147° was used for analysis.

Anal. Calc'd for $\text{C}_{10}\text{H}_{11}\text{NO}_4\text{S}$: C, 49.8; H, 4.6; N, 5.8.

Found: C, 49.7; H, 5.2; N, 5.6.

Acid hydrolysis as described for VII ($\text{R} = -\text{CH}_2\text{COOCH}_3$) gave 2-carboxymethyl-2,5-dihydrothiophene-3,4-dicarboxylic acid (IV, $\text{R} = -\text{CH}_2\text{COOH}$) in 37% yield, m.p. and mixed m.p. 211–213° dec.

2,5-Dihydrothiophene-3,4-dicarboxylic anhydride (XXVIII). A mixture of 0.50 g. of 2,5-dihydrothiophene-3,4-dicarboxylic acid, 5 cc. of benzene and 1.2 cc. of thionyl chloride was refluxed for twenty minutes, gas evolution being complete in ten minutes. Evaporation to dryness *in vacuo* and trituration with petroleum ether gave 0.35 g. (78%) of product, m.p. 164–166°. Recrystallization from benzene did not change the m.p.

Anal. Calc'd for $\text{C}_6\text{H}_4\text{O}_3\text{S}$: C, 46.2; H, 2.6.

Found: C, 46.2; H, 3.0.

4,5-Dihydrothiophene-3,4-dicarboxanilide (XXX, R = H). A mixture of 0.50 g. of 4,5-dihydrothiophene-3,4-dicarboxylic acid (V, $\text{R} = \text{H}$), 5 cc. of benzene, 1.2 cc. of thionyl chloride, and one drop of a solution of one drop of pyridine in 10 cc. of benzene was refluxed for ninety minutes, when gas evolution was complete. The solvent was removed *in vacuo*, leaving an oily acid chloride, which was converted to the dianilide with aniline in benzene; yield, 0.59 g. (63%), m.p. 183–188°. Recrystallization from benzene containing a little acetone afforded white crystals, m.p. 190–192°.

Anal. Calc'd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$: C, 66.7; H, 5.0; N, 8.6.

Found: C, 67.0; H, 5.2; N, 8.3.

3-Hydroxythiophene-3,4-dicarboxylic acid (XXVII, R = H). The cyanohydrin (II, $\text{R} = \text{H}$) from 35 g. of 3-keto-4-carbomethoxythiophene, 70 cc. of acetic acid, and 165 cc. of concentrated hydrochloric acid was refluxed for twenty-two hours. Diluted with 100 cc. of water, the solution was clarified with Norit, then evaporated to dryness *in vacuo*. The residue was dissolved in 100 cc. of water and the evaporation repeated. Extraction with acetone, filtration from ammonium chloride, and evaporation gave 43 g. (quant.) of *cis* and *trans* isomers as a buff-colored solid with a wide melting-point range.

This hydroxy diacid was refluxed two hours with 200 cc. of acetic anhydride, the excess anhydride was removed *in vacuo*, and the residue distilled at 1 mm. in a flask with a wide side arm. The distillate (35 g.), m.p. 113–153°, was recrystallized from benzene giving 14.2 g. (39%) of 2,5-dihydrothiophene-3,4-dicarboxylic anhydride (XXVIII, $\text{R} = \text{H}$), m.p. and mixed m.p. 163–166°. From the filtrate was isolated 8.8 g. (18%) of 3-acetoxythiophene-3,4-dicarboxylic anhydride, m.p. 85–90°.

Anal. Calc'd for $\text{C}_8\text{H}_6\text{O}_5\text{S}$: C, 44.4; H, 3.7.

Found: C, 44.8; H, 4.0.

SUMMARY

1. Dehydration of 2- or 5-alkyl-3-hydroxy-3-cyano-4-carbomethoxythiophanes forms cyano esters with a double bond in the 3,4 position of the thiophene nucleus.

2. Acid hydrolysis of 2- or 5-alkyl-3-cyano-4-carbomethoxy-2,5-dihydrothiophenes gives 2-alkyl-2,5-dihydrothiophene-3,4-dicarboxylic acids.

3. Hydrolysis of 3-cyano-4-carbomethoxy-2,5-dihydrothiophene with strong alkali yields 4,5-dihydrothiophene-3,4-dicarboxylic acid with rearrangement of the double bond to the 2,3 position.

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EXPERIMENTAL CHEMOTHERAPY OF FILARIASIS. IV. THE PREPARATION OF DERIVATIVES OF PIPERAZINE¹

H. W. STEWART, R. J. TURNER, AND J. J. DENTON; S. KUSHNER, L. M.
BRANCONE, W. L. McEWEN, R. I. HEWITT, AND Y. SUBBAROW

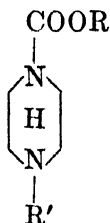
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The general term "filariasis" includes several diseases in man and other vertebrates caused by slender, parasitic, nematode worms located in the circulatory and lymphatic systems, muscles, serous cavities or connective tissues. The microfilariae or prelarval forms are discharged by the adult worms into the blood, lymphatics, or tissues of the hosts. Intermediate hosts (mosquitoes or biting flies) are required for the completion of the life cycle.

In man, several species of filaria are known, the most important being *Wuchereria bancrofti*, *Wuchereria malayi*, and *Onchocerca volvulus*. The former two are widely distributed in Africa, India, China, Japan, the East Indies, and the West Indies. The latter is found only in Africa and certain parts of central America. In animals, filarial diseases are widespread, even in the United States.

Though compounds containing heavy metals, particularly those of antimony (1), and certain cyanine dyes (18) have shown anti-filarial activity in laboratory animals, their use in the treatment of human filariasis leaves much to be desired.

During a recent course of investigation in our laboratories, certain piperazines having the following structure



were found to be quite active as anti-filarial agents on both micro- and macro-filariae.

Of the carbalkoxyl groups studied in this type of molecule, the carbethoxyl seemed to be more effective than the carbomethoxyl, carbo-*n*-butoxyl, or carbo-isobutoxyl. By retaining the carbethoxyl group in the 1-position, the substituent in the 4-position was varied in order to obtain a compound with the greatest apparent antifilarial activity for this type of structure. Of the phenyl, benzyl, and saturated and unsaturated alkyl groups tried in the 4-position, the methyl group gave a compound with maximum antifilarial activity, 1-carbethoxy-4-methylpiperazine.

During this study a number of piperazine derivatives, having the above as

¹ For paper III of this series see Hewitt, Kushner, Stewart, Wallace, White, and SubbaRow.

well as other structures, were prepared. The accompanying table lists compounds synthesized, along with the physical properties for both the piperazine base and its hydrochloride salt. The superscript numbers in the table correspond to the numbered references at the end of the paper, while the superscript letters refer to procedures in the experimental part by which the compounds were synthesized. The last column shows the relative activity of these compounds as antifilarial agents; 1-carbethoxy-4-methylpiperazine, being the most active, is represented by ++. The antifilarial activity is described more completely in paper number II of this series (17). The preparation of other piperazines is presented in the following paper of this series (8).

There are but a few types of compounds known to react with piperazine to produce a reasonable yield of a monosubstituted piperazine; an alkyl chlorocarbonate is one such type of reagent (2, 3). We have utilized this method in preparing several 1-carbalkoxypiperazines which served as intermediates for a number of the compounds reported here. The position of the carbethoxyl group in the monosubstitution product from the reaction of 2-methylpiperazine and ethyl chlorocarbonate was not determined.

Most of the 1-carbalkoxy-4-alkylpiperazines were prepared from the corresponding 1-carbalkoxypiperazines by alkylation, either with an alkyl halide or an alkyl *p*-toluenesulfonate (2). 1-Carbethoxy-4-methylpiperazine, however, was prepared by reductive alkylation of 1-carbethoxypiperazine with formaldehyde in the presence of zinc dust and hydrochloric acid. 1-Carbethoxy-4-phenylpiperazine was synthesized from 1-phenylpiperazine by reacting it with ethyl chlorocarbonate.

Certain 1-alkylpiperazines have been made by Baltzly, *et al.* (3) by the alkylation of 1-benzylpiperazine in the 4-position with subsequent removal of the benzyl group by catalytic hydrogenation (16). A more indirect procedure has been used by Prelog and Stepan (4) for the preparation of 1-methylpiperazine from 1-methyl-4-phenylpiperazine. Moore, Boyle, and Thorn (2) obtained 1-ethylpiperazine from the hydrolysis of 1-carbethoxy-4-ethylpiperazine in concentrated hydrochloric acid. We have used the latter method for preparing the 1-alkylpiperazines reported in this article.

Several media were tried in an attempt to find a more rapid and convenient procedure than that of Moore, *et al.* (2) for the hydrolysis of 1-carbethoxy-4-methylpiperazine. Aqueous acetic acid containing sulfuric acid, 50% sulfuric acid, and aqueous alcoholic sodium hydroxide were all inferior to concentrated hydrochloric acid. One experiment with the latter indicated, however, that a shorter heating period might be used, since about 80% hydrolysis, based on recovered starting material, had occurred after heating for only six hours.

Although Abderhalden and Haas (13) reported the preparation of 1,4-dimethylpiperazine from piperazine and methyl iodide, our attempts to repeat the work were unsuccessful. A quaternary salt appeared to form instead. Several other methods have been reported (14) for the synthesis of this compound. We have prepared 1,4-dimethylpiperazine by the methylation of piperazine with formaldehyde in formic acid (15).

2,3-Diphenyl-5,6-dihydropyrazine was prepared according to Mason (12) by reacting ethylenediamine with benzil. Catalytic hydrogenation of this compound appeared to give only one diastereoisomeric form (the lower-melting, *beta* form) of 2,3-diphenylpiperazine.

EXPERIMENTAL²

Procedure (a). Preparation of 1-alkylpiperazines. The 1-alkylpiperazines, as dihydrochlorides, were prepared by hydrolyzing the appropriate 1-carbethoxy-4-alkylpiperazine with concentrated hydrochloric acid using the method of Moore, Boyle, and Thorn (2). They may be purified by crystallization from absolute ethyl alcohol.

1-Methylpiperazine dihydrochloride. Crystallization of 1-methylpiperazine dihydrochloride from absolute ethyl alcohol gave a product which, when dried at 40°, melted at 82.5–83° (corr.).

Anal. Calc'd for $C_5H_{12}N_2 \cdot 2HCl \cdot H_2O$: Cl, 37.1 Found: Cl, 37.2.

Further crystallization of 1-methylpiperazine dihydrochloride monohydrate and a long period of drying (2 days) at 50° gave a product, which by a Volhard titration corresponded to a partially dehydrated form, that softened at 83° and completely melted at 191°. Two other melting points, 110° (3) and 242° (4), have been reported in the literature.

1-Methylpiperazine. 1-Methylpiperazine was liberated from a solution of the dihydrochloride monohydrate (150 g.) in 100 cc. of water by using 50% sodium hydroxide solution. The base was separated without a solvent. It contained a large amount of dissolved water which was difficult to remove. By placing it repeatedly over fresh portions of solid potassium hydroxide, it was freed of water. On distillation of the dried liquid, 57.5 g. of 1-methylpiperazine was obtained.

1-Isopropylpiperazine dihydrochloride. The dihydrochloride was crystallized from absolute ethyl alcohol.

Anal. Calc'd for $C_7H_{16}N_2 \cdot 2HCl$. C, 41.5; H, 8.0; N, 13.9.

Found: C, 41.2; H, 8.7; N, 14.1.

Procedure (b). Preparation of 1-phenyl-4-methylpiperazine dihydrochloride. To a solution of 43.2 g. of 1-phenyl-4-methylpiperazine (0.245 mole) in 500 cc. of absolute ether, there was added 80 cc. of ethyl alcohol containing 0.49 mole of anhydrous hydrogen chloride. The precipitate was isolated by filtration, washed with ether, and dried at 50°; yield 57.7 g., 94.5% calculated as the anhydrous dihydrochloride. It was purified by crystallization from absolute ethyl alcohol which contained a slight excess of anhydrous hydrogen chloride. When taken in the usual manner the melting point was 193–200° (corr.) with some color produced but no noticeable gases. When immersed at 175°, it melted at 178–182° (corr.) with strong evolution of gas, but with no coloration.

Anal. Calc'd for $C_{11}H_{18}N_2 \cdot 2HCl \cdot H_2O$: Cl, 26.55. Found: Cl, 26.3.

Procedure (c). Preparation of 1,4-dimethylpiperazine (7, 14). The procedure was the same as that used for the methylation of 1-diethylcarbamyloxy-piperazine with formaldehyde and formic acid (8). No solvent was used to extract the oil before distillation. It codistilled somewhat with diethyl ether.

1,4-Dimethylpiperazine dihydrochloride. The dihydrochloride salt was made in the usual manner from an ether solution of the base and anhydrous hydrochloric acid and crystallized from methyl alcohol-isopropyl acetate. It was dried at 50°.

Anal. Calc'd for $C_6H_{14}N_2 \cdot 2HCl \cdot 2/3H_2O$: C, 36.19; H, 8.77; N, 14.07; Cl, 35.61; H_2O , 6.03.

Found: C, 36.0; H, 8.6; N, 14.1; Cl, 35.6; H_2O , 5.98 (Karl Fischer).

² The microchemical analyses were carried out by O. E. Sundberg, M. E. Nielsen, and I. H. Prokul.

Procedure (d). Preparation of 1-carbalkoxypiperazines and 1,4-dicarbalkoxypiperazines in a water solution. The procedure was that used by Moore, Boyle, and Thorn (2) for the reaction of ethyl chlorocarbonate with piperazine in a buffered water solution. The yields of the 1,4-dicarbalkoxypiperazines given in Table I are based on the amount of starting piperazine.

1-Carbomethoxypiperazine.

Anal. Calc'd for $C_6H_{12}N_2O_2$: C, 50.0; H, 8.3; N, 19.5.

Found: C, 49.4; H, 8.1; N, 18.9.

1,4-Dicarbomethoxypiperazine.

Anal. Calc'd for $C_8H_{14}N_2O_4$: N, 13.9. Found: N, 13.7.

1-Carbo-n-butoxypiperazine.

Anal. Calc'd for $C_9H_{18}N_2O_2$: C, 58.2; H, 9.7.

Found: C, 58.7; H, 10.0.

1,4-Di(carbo-n-butoxy)piperazine.

Anal. Calc'd for $C_{14}H_{26}N_2O_4$: N, 9.8. Found: N, 9.7.

1-Carboisobutoxypiperazine.

Anal. Calc'd for $C_9H_{18}N_2O_4$: C, 58.2; H, 9.7; N, 15.1.

Found: C, 58.0; H, 10.0; N, 15.0.

1,4-Di(carboisobutoxy)piperazine.

Anal. Calc'd for $C_{14}H_{26}N_2O_4$: C, 58.7; H, 9.1; N, 9.8.

Found: C, 58.8; H, 9.4; N, 9.7.

1-Carbethoxy-2-(or 3)methylpiperazine. To 17 g. of 2-methylpiperazine was added 150 cc. of water and enough hydrochloric acid to bring the solution to pH 3. During a period of one hour, 18 cc. of ethyl chlorocarbonate was added along with sodium acetate to maintain a pH of 3 to 3.5. The solution was extracted with ether and the extract was discarded. The aqueous layer was then cooled, saturated with potassium carbonate and extracted thoroughly with ether. This ethereal solution was dried over magnesium sulfate and then distilled; yield, 10.1 g. of a yellow oil.

Anal. Calc'd for $C_8H_{16}N_2O_2$: N, 16.3. Found: N, 16.4.

1,4-Dicarbethoxy-2-methylpiperazine. The preparation of 1,4-dicarbethoxy-2-methylpiperazine was carried out in a slightly different manner. To 20 g. of 2-methylpiperazine dihydrochloride was added a solution of 16.5 g. of potassium hydroxide pellets in 100 cc. of water. Then a total of 30 cc. of ethyl chlorocarbonate was added in six 5-cc. portions, while at the same time there was slowly added another 16.5-g. portion of potassium hydroxide in 100 cc. of water, so that the reaction remained slightly alkaline to phenolphthalein. The oil that separated was taken up in ether, dried over magnesium sulfate and distilled; yield 21.7 g.

Anal. Calc'd for $C_{11}H_{20}N_2O_4$: N, 11.5. Found: N, 11.3.

Procedure (e). Preparation of 1-carbethoxypiperazine hydrochloride and 1,4-dicarbethoxypiperazine in an 86% ethyl alcohol solution. This procedure is a modification of that used by Baltzly and co-workers (3). Ten moles (860 g.) of anhydrous piperazine (b.p. 142–147°) was dissolved in 5 liters of 85% ethanol. To this was added, with mechanical stirring, 953 cc. (10 moles) of ethyl chlorocarbonate, keeping the temperature below 50° by means of external cooling; this addition required about 50 minutes. The solution was stirred for one-half hour after the addition of ethyl chlorocarbonate, and then was made acid to Congo Red with concentrated hydrochloric acid.


The piperazine dihydrochloride which had precipitated was washed with alcohol, and dried at 50°. The total amount of piperazine dihydrochloride collected was 525 g. (3.3 moles), 33%.

The filtrate from the piperazine dihydrochloride was treated with 100 g. of Darco and clarified. The clarified filtrate was evaporated *in vacuo* to a volume of 1 liter, and the material which precipitated upon cooling was collected and washed with isopropyl acetate. By this method, 910 g. (4.7 moles) of 1-carbethoxypiperazine hydrochloride, m.p. 145–148°,

TABLE I
PIPERAZINE DERIVATIVES

COMPOUND	R ₁	R ₂	B.P. OF BASE, °C.	MM.	YIELD, %	M.P. OF HCl, °C.	ACTIVITY
I	CH ₃	H	134-136*, 4	760	74*, 4	82.5-83*, 2, 4	-
II	CH ₃	CH ₃	131-133*, 7	760	96.6*	251.5-253*, 7 (dec.)	-
III	CH ₃	CH ₃ CH ₂ N(CH ₃) ₂			70*	262-264	-
IV	C ₂ H ₅	H			58*		-
V	(CH ₃) ₂ CH	H		15	90*	274-275 (dec.)	-
VI	C ₄ H ₉	H	161-164*, 5, 6	8	31.5*	245-247*, 8	+
VII	C ₄ H ₉	CH ₃	130-131*, 4, 7		70.57	180-182* (dec.)	-
					94.5 ^b	178-182* (dec.)	
VIII	CO ₂ CH ₃	H	112-116	7	37 ^d		-
IX	CO ₂ CH ₃	CH ₃	116-121 (m.p.)		16*		-
X	CO ₂ CH ₃	CO ₂ CH ₃	163	11	2 ^d		-
XI	CO ₂ C ₂ H ₅	H			47*	156.5-157*, 9, 3	+
XII	CO ₂ C ₂ H ₅	CH ₃	97-98*	8	96 ^f		+
					96 ^f	168.5-169*	
XIII	CO ₂ C ₂ H ₅	C ₂ H ₅	132	28	82*		+
XIV	CO ₂ C ₂ H ₅	<i>n</i> -C ₄ H ₇	136	16	73*	189-192	+
XV	CO ₂ C ₂ H ₅	<i>iso</i> -C ₄ H ₇	138-144	19	75*		+
XVI	CO ₂ C ₂ H ₅	<i>n</i> -C ₄ H ₉	139-140	8	64*		+
XVII	CO ₂ C ₂ H ₅	<i>iso</i> -C ₄ H ₉	93.5-94	1	63*		+
XVIII	CO ₂ C ₂ H ₅	<i>sec</i> -C ₄ H ₉	139-147	18	40*	218-221 (dec.)	-
XIX	CO ₂ C ₂ H ₅	<i>n</i> -C ₇ H ₁₅	159-161*	4	86 ^b		+
XX	CO ₂ C ₂ H ₅	CH ₂ =CHCH ₃	113-115*	6	81.7 ^b		-
XXI	CO ₂ C ₂ H ₅	CH ₂ CH ₂ OH	175-177	12	72*		-
XXII	CO ₂ C ₂ H ₅	CH ₃ CO ₂ C ₂ H ₅	123-125	2	75*		-
XXIII	CO ₂ C ₂ H ₅	C ₆ H ₅	61-61.5* (m.p.)		92 ^a	197-198* (dec.)	-
XXIV	CO ₂ C ₂ H ₅	C ₆ H ₅ CH ₃			86 ^b	218-218.5*	-

TABLE I—Continued

	$\text{CO}_2\text{C}_6\text{H}_5$	COC_2H_5		3	8°		
XXV			131-133°, 2, 10, 11				-
XXVI			45-46 (m.p.)	10	46 ^d		-
XXVII	$\text{CO}_2\text{C}_6\text{H}_5(n)$	H	141-143	10	5.2 ^d		-
XXVIII	$\text{CO}_2\text{C}_6\text{H}_5(n)$	$\text{CO}_2\text{C}_4\text{H}_9(n)$	205-208	13	52 ^d		-
XXIX	$\text{CO}_2\text{C}_6\text{H}_5(iso)$	H	138-142	15	7.3 ^d		-
	$\text{CO}_2\text{C}_6\text{H}_5(iso)$	$\text{CO}_2\text{C}_4\text{H}_9(iso)$	203-205				
	MISCELLANEOUS						
XXX		$(\text{C}_2\text{H}_5\text{O}_2\text{CN} \begin{array}{c} \diagup \text{H} \diagdown \\ \text{N} \end{array})_2 \text{CH}_3$	61.5-62.5* (m.p.)	95.7 ^a			+
XXXI		$(\text{C}_2\text{H}_5\text{CO}_2\text{N} \begin{array}{c} \diagup \text{H} \diagdown \\ \text{NCH}_2 \end{array})_2$	258-262* 80-80.5 (m.p.)	12	86.4 ^h		-
XXXII		$(\text{CH}_3\text{N} \begin{array}{c} \diagup \text{H} \diagdown \\ \text{N} \end{array})_2 \text{SO}_2$	89-90.5 (m.p.)		32 ^k		-
XXXIII					72.5 ^j	310-311* (dec.)	-
XXXIV	$\text{C}_2\text{H}_5\text{O}_2\text{CN} \begin{array}{c} \diagup \text{H} \diagdown \\ \text{NH} \end{array}$	$\begin{array}{c} \diagup \text{CH}_3 \diagdown \\ \text{CH}_3 \end{array}$	127-129	18	60 ^d		-
XXXV	$\text{C}_2\text{H}_5\text{O}_2\text{CN} \begin{array}{c} \diagup \text{H} \diagdown \\ \text{N} \end{array}$	$\begin{array}{c} \diagup \text{CH}_3 \diagdown \\ \text{CH}_3 \end{array}$	173-175	16	74 ^d		+

* Corrected temperature.

was obtained; 47%. A portion was crystallized from absolute ethyl alcohol to the constant melting point 156.5–157° (corr.). The pH of a 1% water solution was 5.1 at 25°; its approximate solubility was 360 g./100 cc. of water at 25°.

Anal. Calc'd for $C_7H_{14}N_2O_2 \cdot HCl$: C, 43.17; H, 7.77; N, 14.39; Cl, 18.21.

Found: C, 43.3; H, 7.9; N, 14.6; Cl, 17.9.

1,4-Dicarbethoxypiperazine was obtained from the alcohol-isopropyl acetate filtrate by concentration of it *in vacuo* and recrystallization of the residue from petroleum ether. The yield of 1,4-dicarbethoxypiperazine, m.p. 43.5–45.5°, was 184 g. (0.8 mole); 8% based on starting piperazine. A portion was crystallized from petroleum ether (b.p. 35–60°) to the constant melting point 45–46° (corr.); b.p. 131–133° (corr.)/3 mm. The pH of a 1% water solution was 6.5; approximate solubility 4.3 g./100 cc. water at 25°.

Procedure (f). Preparation of 1-carbethoxy-4-methylpiperazine. To a 5-liter, 3-necked flask there were added 291.8 g. (1.5 moles) of 1-carbethoxypiperazine hydrochloride, 600 cc. of water, and 196.5 g. (3.0 moles) of zinc dust. The flask was immersed in an ice-bath and while the temperature of the solution was kept at 10–15°, 192 g. (2.3 moles) of 36% aqueous formaldehyde solution was added with good agitation over a period of 15 minutes.

At the end of this time, 600 cc. of concentrated hydrochloric acid (sp. gr. 1.18, 7.5 moles) was added slowly, keeping the temperature below 20°. After the addition of the hydrochloric acid, which required about one hour, the solution was stirred for 10 hours at 20–25° without cooling.

Aqueous sodium hydroxide solution (50%) was added with stirring until soluble sodium zincate was obtained and no more oil separated, while the temperature of the solution was kept below 20°. The oil layer was separated and the lower caustic layer was extracted six times with diethyl ether. The oil and ether extracts were combined and dried over sodium sulfate. After removal of the ether the product was distilled under reduced pressure. The base was found to be soluble in water.

Anal. Calc'd for $C_8H_{16}N_2O_2$: C, 55.80; H, 9.30; N, 16.28.

Found: C, 56.1; H, 9.29; N, 16.1.

The hydrochloride was prepared by introducing anhydrous hydrochloric acid into an ether solution of the base. It was purified by crystallization from absolute ethyl alcohol. The pH of a 1% water solution was 4.40 at 25°; its approximate solubility was 280 g./100 cc. of water at 25°.

Anal. Calc'd for $C_8H_{16}N_2O_2 \cdot HCl$: C, 46.03; H, 8.21; N, 13.42; Cl, 16.98.

Found: C, 46.5; H, 8.1; N, 13.3; Cl, 17.1.

Procedure (g). Preparation of 1-carbalkoxy-4-alkylpiperazines. The procedure was that used by Moore, Boyle, and Thorn (2) for the preparation of 1-carbethoxy-4-ethylpiperazine. The 1-carbalkoxypiperazine was treated with the appropriate alkyl ester of *p*-toluenesulfonic acid.

1-Carbomethoxy-4-methylpiperazine.

Anal. Calc'd for $C_7H_{14}N_2O_2$: C, 53.1; H, 8.9; N, 11.4.

Found: C, 52.7; H, 8.5; N, 11.0.

1-Carbethoxy-4-n-propylpiperazine. The free base was not analyzed. The hydrochloride was prepared in the usual manner and crystallized from absolute ethyl alcohol.

Anal. Calc'd for $C_{10}H_{20}N_2O_2 \cdot HCl$: C, 50.7; H, 8.9; N, 11.8.

Found: C, 50.6; H, 9.3; N, 11.7.

1-Carbethoxy-4-isopropylpiperazine.

Anal. Calc'd for $C_{10}H_{20}N_2O_2$: C, 60.0; H, 10.0.

Found: C, 60.1; H, 9.9.

1-Carbethoxy-4-n-butylpiperazine.

Anal. Calc'd for $C_{11}H_{22}N_2O_2$: C, 61.7; H, 10.3; N, 13.1.

Found: C, 61.4; H, 10.3; N, 13.5.

1-Carbethoxy-4-isobutylpiperazine.

Anal. Calc'd for $C_{11}H_{23}N_2O_2$: C, 61.68; H, 10.28; N, 13.08.

Found: C, 61.6; H, 10.5; N, 13.3.

1-Carbethoxy-4-sec-butylpiperazine. The free base was not analyzed. The hydrochloride was prepared in the usual manner and crystallized from absolute ethyl alcohol.

Anal. Calc'd for $C_{11}H_{23}N_2O_2 \cdot HCl$: C, 52.6; H, 9.2; N, 11.1.

Found: C, 52.3; H, 9.4; N, 10.6.

Procedure (h). Reaction of 1-carbethoxypiperazine with alkyl halides. The halides used were *n*-heptyl bromide, allyl chloride, benzyl chloride, methylene bromide, and ethylene bromide. One mole of 1-carbethoxypiperazine hydrochloride, three moles of sodium bicarbonate, 300 cc. of 95% ethyl alcohol, and one mole of the halide (1.2 moles with allyl chloride and 0.5 mole with methylene bromide or ethylene bromide) were heated, while stirring, at the refluxing temperature for seven hours. (The reaction with benzyl chloride was refluxed for only two hours. The reaction with allyl chloride was not refluxed but was stirred at 45–50°.)

Most of the alcohol was removed by distillation and then the product was stirred into 1 liter of water to dissolve the inorganic salts. The solution was made strongly basic to phenolphthalein with potassium carbonate. The oil which separated was extracted with ether, dried over sodium sulfate, and after the ether was removed, was distilled as indicated in Table I.

1-Carbethoxy-4-benzylpiperazine. The free base was not distilled but the hydrochloride salt was prepared in the usual manner and crystallized (113 g.) from absolute ethyl alcohol (360 cc.).

Anal. Calc'd for $C_{14}H_{20}N_2O_2 \cdot HCl$: C, 59.05; H, 7.43; N, 9.84; Cl, 12.46.

Found: C, 58.9; H, 7.6; N, 9.99; Cl, 12.3.

1-Carbethoxy-4-allylpiperazine. In this reaction, in order to minimize the loss of the volatile allyl chloride by entrainment with the evolved carbon dioxide, the reaction was heated to the boiling point and then cooled before the allyl chloride was added.

Anal. Calc'd for $C_{11}H_{19}N_2O_2$: C, 60.54; H, 9.15; N, 14.13.

Found: C, 60.5; H, 8.9; N, 14.3.

Bis(1-carbethoxy-4-piperazyl)methane. This compound distilled with some decomposition at 4 mm. A quantity of 124 g. was crystallized from 250 cc. of petroleum ether (b.p. 35–60°) to the constant melting point 61.5–62.5° (corr.). The pH of a 1% water solution was 9.8 at 27°; approximate solubility was 4.7 g./100 cc. water at 27°. It gave oily salts with hydrochloric, sulfuric, and phosphoric acids.

Anal. Calc'd for $C_{18}H_{28}N_4O_4$: C, 54.86; H, 8.59; N, 17.06.

Found: C, 54.8; H, 8.7; N, 17.0.

1,2-Bis(1-carbethoxy-4-piperazyl)ethane. After distillation, 125 g. of this compound was crystallized from 350 cc. of mixed hexanes, m.p. 80–80.5° (corr.). The pH of a 1% water solution was 8.7 at 27°; approximate solubility was 1.9 g./100 cc. water at 27°. When treated with a small amount of water it dissolved completely and then precipitated, probably as a less soluble hydrate; this redissolved after the addition of more water.

Anal. Calc'd for $C_{18}H_{28}N_4O_4$: C, 56.13; H, 8.83; N, 16.36.

Found: C, 56.1; H, 8.7; N, 16.1.

Procedure (i). Preparation of 1-carbethoxy-4-phenylpiperazine. To 150 cc. of absolute ethyl alcohol were added 54.7 g. of 1-phenylpiperazine hydrochloride (0.275 mole), 29.8 g. of ethyl chlorocarbonate (0.275 mole), and 69.2 g. of sodium bicarbonate (0.83 mole). The reaction was heated, while stirring, at the refluxing temperature for three hours. The alcohol was removed by distillation, 500 cc. of warm water (above 60°) was added and the reaction was stirred till the inorganic salts had dissolved. A small amount of sodium hydroxide was added to make the reaction basic to phenolphthalein and the oil-water slurry was cooled while stirring. The solid was isolated by filtration, washed with water until neutral and dried at room temperature. The yield was 59.2 g. It was crystallized from petroleum ether (2.3 cc./g.) (b.p. 35–60°); m.p. 61–61.5° (corr.).

Anal. Calc'd for $C_{11}H_{15}N_3O_2$: C, 66.64; H, 7.74; N, 11.96.

Found: C, 66.9; H, 7.5; N, 11.9.

The hydrochloride was prepared from anhydrous hydrogen chloride and an absolute ethyl alcohol solution of the base. It was crystallized from the same solvent (5.8 cc./g.). The salt was insoluble in water due to hydrolysis but was readily soluble in very dilute hydrochloric acid.

Anal. Calc'd for $C_{11}H_{15}N_3O_2 \cdot HCl$: C, 57.65; H, 7.07; N, 10.35; Cl, 13.09.

Found: C, 58.4; H, 7.0; N, 10.2; Cl, 12.6.

Procedure (j). Preparation of *beta*-2,3-diphenylpiperazine³ (12). The 2,3-diphenyl-5,6-dihydropyrazine used in this procedure was prepared by the method used by Mason (12); yield 92%.

To 350 cc. of absolute ethyl alcohol were added 150 g. of 2,3-diphenyl-5,6-dihydropyrazine (0.63 mole) and 15 g. of copper chromite. This was hydrogenated in an autoclave at 150° and 1,000 lbs. until no more hydrogen was taken up (two hours). After cooling, the catalyst was removed and the filtrate was heated and water added to give 50% aqueous alcohol. When cool, the crystals which separated were washed with 50% aqueous alcohol and dried at 50°; yield 131.2 g.; m.p. 92.5–101° (corr.). Another crystallization from 50% aqueous alcohol gave 110.4 g. (72.5%); m.p. 108–109° (corr.). The filtrate, on dilution to give 25% aqueous alcohol, gave 6.4 g.; m.p. 97.5–103°. No evidence of the *alpha* isomer, m.p. 122–123°, was found.

The dihydrochloride (12) was prepared by adding anhydrous hydrogen chloride to a solution of the base in absolute ethyl alcohol. The dihydrochloride was insoluble in ethyl alcohol. Two crystallizations from water gave a product which melted at 310–311° (dec.) (corr.). The pH of a 1% water solution was 2.04 at 25°; its approximate solubility was 11.4 g./100 of cc. water at 25°.

Anal. Calc'd for $C_{11}H_{15}N_3 \cdot 2HCl$: C, 61.73; H, 6.48; N, 9.00; Cl, 22.78.

Found: C, 61.6; H, 6.5; N, 9.04; Cl, 22.6.

Some of the base was liberated from a small amount of the dihydrochloride by the addition of dilute sodium hydroxide to a water solution of the salt. After washing and drying, the base melted at 110–110.5° (corr.).

Procedure (k). Preparation of 1,1'-sulfonyl-bis(4-methylpiperazine). Ten g. of 1-methylpiperazine (0.1 mole) was dissolved in 30 g. of chloroform and immersed in an ice-bath; to the chilled chloroform solution, 4 g. of sulfonyl chloride (0.025 mole), technical grade, was cautiously added. The temperature of the solution was kept below 40° throughout the addition of sulfonyl chloride.

The chloroform was removed by evaporation on a steam-bath. To the residual liquid dilute sodium hydroxide was added until a pink spot was obtained on Brilliant Yellow test paper. The aqueous solution was extracted thoroughly with chloroform, which was subsequently evaporated to leave an orange oil; yield 2.1 g. (32%, based on sulfonyl chloride). This solidified on standing and was crystallized from mixed hexanes.

Anal. Calc'd for $C_{10}H_{18}N_4O_2S$: C, 45.8; H, 8.4; N, 21.3; S, 12.2.

Found: C, 45.8; H, 8.4; N, 21.0; S, 12.2.

Procedure (l). Preparation of 1-methyl-4-(2-dimethylaminoethyl)piperazine. To 100 cc. of 95% ethyl alcohol there were added 10 g. of N,N-dimethyl-2-chloroethylamine hydrochloride (0.07 mole), 13.4 g. of 1-methylpiperazine dihydrochloride monohydrate (0.07 mole), and 14.9 g. of sodium carbonate (0.14 mole). The reaction was stirred at the refluxing temperature for 18 hours. The inorganic salts were removed by filtration and the product was isolated from filtrate by concentration and crystallization from ethyl alcohol, m.p. 262–264°.

Anal. Calc'd for $C_9H_{21}N_3 \cdot 2HCl$: C, 44.3; H, 9.4; N, 17.2.

Found: C, 44.5; H, 9.6; N, 17.4.

³ This compound was prepared by Virginia (Mrs. J. J.) Lawson.

SUMMARY

Several new derivatives of piperazine have been prepared. The activity of these and other derivatives of piperazine as antifilarial agents has been reported.

BOUND BROOK, NEW JERSEY
PEARL RIVER, NEW YORK

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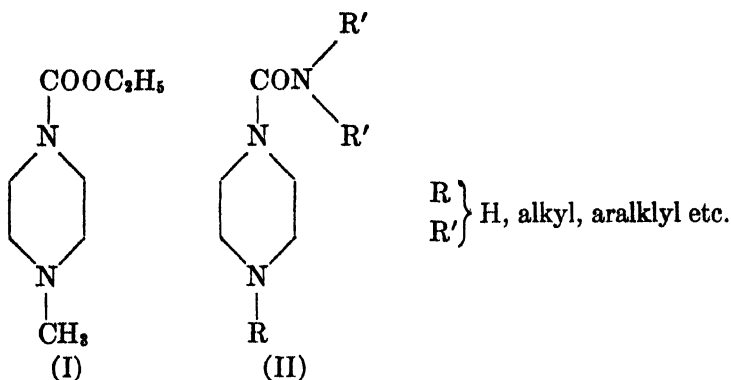
EXPERIMENTAL CHEMOTHERAPY OF FILARIASIS. V. THE PREPARATION OF DERIVATIVES OF PIPERAZINE

S. KUSHNER, L. M. BRANCONE, R. I. HEWITT, W. L. McEWEN, AND
Y. SUBBAROW; H. W. STEWART, R. J. TURNER, AND J. J. DENTON

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In a preceding paper we have shown that certain carbethoxypiperazines are active filaricides. Of these the most important was 1-carbethoxy-4-methylpiperazine (I), with high antifilarial activity (1).

In the syntheses of a number of carbamyl and other derivatives of piperazine we have found that 1-alkyl-4-dialkylcarbamylpiperazines (II) give the most pronounced oral activity.



In Table I are listed the piperazine derivatives and their relative activity (2). 1-Guanyl-4-carbethoxypiperazine (V) is an active compound, but when converted to 1,4-diguanylpiperazine (VI) it becomes inactive.

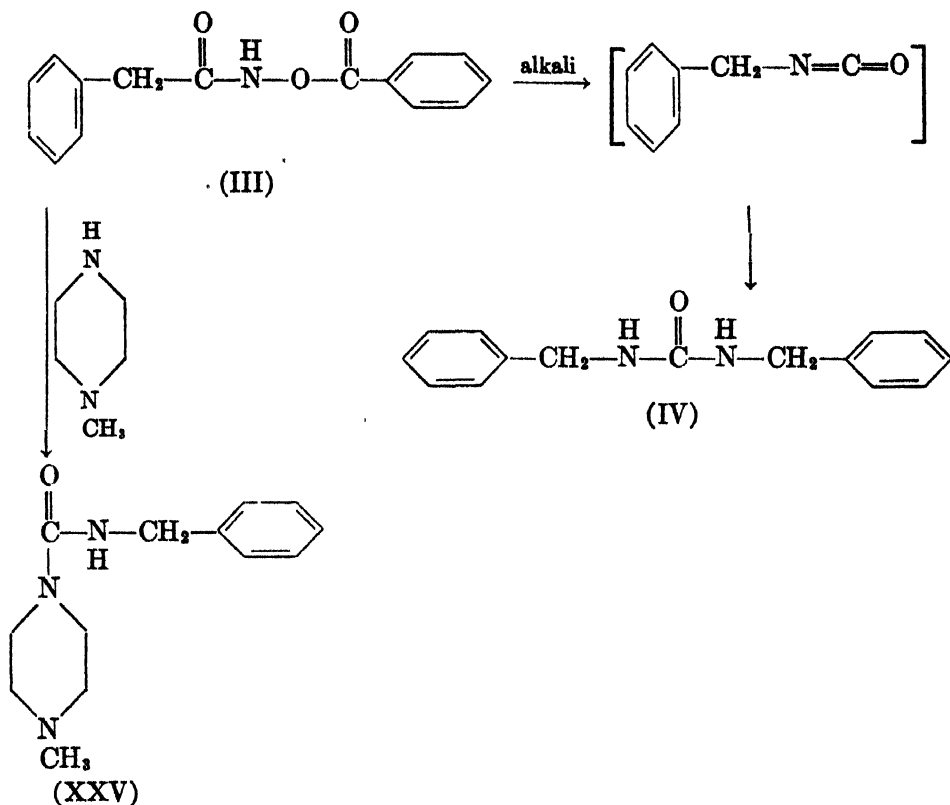
Activity reaches maximum in 1-dimethylcarbamyl-4-methylpiperazine (XIX), and 1-diethylcarbamyl-4-methylpiperazine (XXI). As in the 1-carbethoxy-4-alkyl series it will be noted that activity decreases as the size of the substituents increases.

Preliminary observations on twenty-six human patients infected with filariasis demonstrate that 1-diethylcarbamyl-4-methylpiperazine (XXI) produces a marked and rapid effect against microfilariae in the peripheral blood, and a suggestive effect against adult filariae. These and further results from human cases will be reported elsewhere (3). This compound also shows ascaricidal activity in the dog (4).

The 1-substituted carbamyl-4-alkylpiperazines were prepared by reacting the required carbamyl chloride usually in water or chloroform with the corresponding alkyl piperazine prepared by the method of Moore and co-workers (5). For large scale preparative work as in the case of 1-diethylcarbamyl-4-methylpiperazine (XXI), diethylcarbamyl chloride was reacted with piperazine in alcohol to

give 1-diethylcarbamyloxy-piperazine (XII) which was then treated with formaldehyde and formic acid to give the required product in good yield.

The synthesis of 1-benzylcarbamyloxy-4-methylpiperazine was effected by a modification of the procedure of James (6) wherein the benzoate of phenylacethydroxamic acid (III), when heated with aqueous alkali gives symmetrical dibenzylurea (IV) presumably through the intermediate benzylisocyanate.



Instead of heating the benzoate (III) with alkali, two moles of 1-methylpiperazine are added, one mole causes the intermediate formation of the isocyanate which immediately reacts with the remaining 1-methylpiperazine to give the desired 1-benzylcarbamyloxy-4-methylpiperazine (XXV).

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EXPERIMENTAL

1-Carboethoxy-4-quanylpiperazine sulfate (V). A mixture of 15.7 g. (0.12 mole) of 1-carboethoxypiperazine and 13.9 g. (0.1 mole) of methylisothiurea sulfate in 50 ml. of 65% alcohol was refluxed for 2.4 hours until no more methylmercaptan was evolved and then concentrated to dryness. The resinous mass crystallized when triturated with ether, wt. 19.1 g. It melted at 171° when recrystallized from alcohol-ether.

Anal. Calc'd for $\text{C}_{16}\text{H}_{24}\text{N}_4\text{O}_6\text{S}$: N, 22.5. Found: N, 23.0.

1-Carboethoxy-4-nitrosopiperazine (VII). To a stirred mixture, maintained at -10° , of

TABLE I
1,4-DISUBSTITUTED PIPERAZINES

R	$ \begin{array}{c} \text{CH}_2-\text{CH}_2 \\ \diagup \quad \diagdown \\ \text{R}-\text{N} \quad \text{N}-\text{R}' \\ \diagdown \quad \diagup \\ \text{CH}_2-\text{CH}_2 \\ \text{R}' \end{array} $	B. P. °C. PRESSURE MM.	M. P. °C.	Yield, %	Activity*
V C ₂ H ₅ OOC—	$ \begin{array}{c} \text{NH} \\ \parallel \\ -\text{C}-\text{NH}_2 \end{array} $		171	77	+
VI H ₂ N—C— \parallel NH	$ \begin{array}{c} \text{NH} \\ \parallel \\ -\text{C}-\text{NH}_2 \text{ (13)} \end{array} $		>300	28	—
VII C ₂ H ₅ OOC—	—N=O	180-183 14		38	—
VIII C ₂ H ₅ OOC—	—NH ₂		190-191 ^B	43	—
IX C ₂ H ₅ OOC—	$ \begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{NH}_2 \end{array} $		116-161.5 ^A	73	—
X C ₂ H ₅ OOC—	—CON(C ₂ H ₅) ₂	163-167 3		66	—
XI H—	—CON(CH ₃) ₂	144-146 15		35	D
XII H—	—CON(C ₂ H ₅) ₂	113.5-115.5 ^A 3	147-151 ^B	34	—

TABLE I—Continued

XIII H—	—CON[CH(CH ₃) ₂] ₂	$\frac{146}{9}$		26	—
XIV H—	—CON(n—C ₄ H ₉) ₂	$\frac{158-162}{5}$		40	—
XV H—	—CON(l—C ₄ H ₁₁) ₂	$\frac{200-202}{35}$		17	—
XVI (C ₂ H ₅) ₂ NOC—	—CON(C ₂ H ₅) ₂	$\frac{174-178}{2}$	55.7-56.0 ^A	15	—
XVII CH ₃ —	$\begin{array}{c} \text{O} \\ \parallel \\ \text{—C—NH}_2 \end{array}$		189-190 ^{A,B}	72	—
XVIII CH ₃ —	$\begin{array}{c} \text{S} \\ \parallel \\ \text{—C—NH}_2 \end{array}$		131-132 ^{A,B}	64	—
XIX CH ₃ —	—CON(CH ₃) ₂		180-181 ^B	33	++
XX CH ₃ —	—CONHC ₂ H ₅		177 dec. ^B	33	+
XXI CH ₃ —	—CON(C ₂ H ₅) ₂	$\frac{108.5-111^A}{3}$	156.5-157 ^{A,B} 47-49 ^A	93 ^C 65 80	++
XXII CH ₃ —	—CON[CH(CH ₃) ₂] ₂		200-203 ^B	61	+
XXIII CH ₃ —	—CON(n—C ₄ H ₉) ₂		151-152 ^B	30	—

TABLE I—Continued

R	$ \begin{array}{c} \text{CH}_2\text{---CH}_2 \\ \diagup \quad \diagdown \\ \text{R---N} \quad \text{N---R'} \\ \diagdown \quad \diagup \\ \text{CH}_2\text{---CH}_2 \\ \text{R'} \end{array} $	B. P. °C. PRESSURE MM.	M. P. °C.	YIELD, %	ACTIVITY*
XXIV CH ₃ —	$ \begin{array}{c} \text{H} \\ \\ \text{---C---N---C}_6\text{H}_5 \\ \\ \text{O} \end{array} $		126-130	90	—
XXV CH ₃ —	$ \begin{array}{c} \text{H} \\ \\ \text{---C---N---CH}_2\text{C}_6\text{H}_5 \\ \\ \text{O} \end{array} $		188-192	54	—
XXVI CH ₃ —	$ \begin{array}{c} \text{H} \\ \\ \text{---C---N---} \begin{array}{c} \diagup \quad \diagdown \\ \text{CH}_2 \quad \text{CH}_2 \\ \diagdown \quad \diagup \\ \text{N---CH}_3 \end{array} \\ \\ \text{O} \end{array} $		303-304	60	—
XXVII CH ₃ —	$ \begin{array}{c} \text{O} \\ \\ \text{---C---N---} \begin{array}{c} \diagup \quad \diagdown \\ \text{CH}_2 \quad \text{CH}_2 \\ \diagdown \quad \diagup \\ \text{O} \end{array} \\ \\ \text{O} \end{array} $	$ \frac{178-179}{17} $	52-55	61	+
XXVIII i-C ₃ H ₇ —	—CON(C ₂ H ₅) ₂	$ \frac{160}{16} $	206-208.5	32	—

* Tested against microfilaria in cotton rats.

A Corrected temperatures.

B Hydrochloride.

C Prepared by three methods described below.

D Not tested.

189 g. (1.2 moles) of 1-carbethoxypiperazine, 480 g. of ice, and 300 ml. of concentrated hydrochloric acid was added over a period of one and one-half hours 168 g. of sodium nitrite dissolved in the minimum amount of water. The solution was neutralized with ice-cold alkali and then extracted with successive portions of ether until the yellow color was removed from the aqueous solution. The combined ethereal extracts were dried over magnesium sulfate and then fractionated under reduced pressure. The fraction boiling at 180–183° (14 mm.) was collected as 1-carbethoxy-4-nitrosopiperazine (VII), wt. 84.8 g.

Anal. Calc'd for $C_7H_{12}N_2O_2$: C, 44.9; H, 6.9.

Found: C, 45.4; H, 6.6.

1-Carbethoxy-4-aminopiperazine hydrochloride (VIII). To a stirred slurry (kept at 25–30°) of 7 g. (0.037 mole) of 1-carbethoxy-4-nitrosopiperazine and 19 g. of zinc dust was added over a period of two hours 54 ml. of 85% acetic acid. The reaction mixture was then heated for one hour at 60°, filtered, and the filtrate evacuated to dryness in a water-bath. The residue was made strongly alkaline with concentrated potassium hydroxide solution and extracted thoroughly with ether after saturating the solution with potassium carbonate. The ethereal extracts were dried over magnesium sulfate and evacuated to an oil. The oil was dissolved in ether, filtered from insoluble impurities, and the amine hydrochloride was precipitated from ether by a stream of dry hydrogen chloride, wt. 3.3 g. After recrystallization from alcohol-ether it melted at 190–191°.

Anal. Calc'd for $C_7H_{12}ClN_2O_2$: C, 40.1; H, 7.6; N, 20.0.

Found: C, 40.6; H, 7.8; N, 19.9.

1-Carbamyl-4-carbethoxypiperazine (IX). A solution of 82 g. (1 mole) of potassium cyanate in 75 ml. of water was added to a solution of 195 g. (1 mole) of 1-carbethoxypiperazine hydrochloride in 125 ml. of water. The mixture of solutions was agitated for a few minutes and after standing at room temperature for twenty-four hours it was evaporated to dryness. The residue was extracted with 400 ml. of absolute alcohol, acidified with hydrochloric acid and then evaporated to 125 ml. Upon cooling, crystallization occurred. The solid was recrystallized from alcohol with charcoaling, wt. 146.2 g., m.p. 161–162° (corr.).

Anal. Calc'd for $C_8H_{13}N_3O_2$: C, 47.7; H, 7.5; N, 20.8.

Found: C, 47.4; H, 7.6; N, 20.6.

1-Carbamyl-4-methylpiperazine hydrochloride (XVII). This was prepared in the same manner as compound (IX) with the use of 1-methylpiperazine; m.p. 189–190° (corr.) after recrystallization from alcohol.

Anal. Calc'd for $C_8H_{14}ClN_2O$: N, 23.3; Cl, 19.7.

Found: N, 23.0; Cl, 19.4.

1-Thiocarbamyl-4-methylpiperazine hydrochloride (XVIII). This was prepared similarly to compound (IX), with corresponding use of potassium thiocyanate; m.p. 131–132° (corr.) after recrystallization from alcohol.

Anal. Calc'd for $C_8H_{14}ClN_2S$: C, 36.3; H, 7.2; N, 21.5; S, 16.4.

Found: C, 36.6; H, 7.3; N, 21.8; S, 16.5.

1-Benzylcarbamyl-4-methylpiperazine hydrochloride (XXV). A solution of 10 g. (0.04 mole) of the benzoate of phenylacethydroxamic acid (6), 50 ml. of water, and 8 g. (0.08 mole) of 1-methylpiperazine was heated for seven minutes on a steam cone. A cloudiness developed which was increased by an addition of 50 ml. of water. After saturating with potassium carbonate the 1-benzylcarbonyl-4-methylpiperazine was extracted thoroughly with ether, dried over magnesium sulfate, filtered, and precipitated as its hydrochloride by a stream of dry hydrogen chloride. The oil crystallized on scratching and weighed 5 g. After recrystallization from alcohol it melted at 188–192°.

Anal. Calc'd for $C_{15}H_{20}ClN_2O$: C, 58.1; H, 7.1.

Found: C, 58.1; H, 7.5.

1-Methyl-4-[(4-morpholine)carbonyl]piperazine (XXVII). To a stirred ice-cold solution of 17.9 g. of 1-methylpiperazine dihydrochloride monohydrate, 13.8 g. of 85% potassium

hydroxide, and 150 ml. of water was added simultaneously over a period of ten minutes 15.5 g. of 4-morpholinecarbamylic chloride (7) and 6.9 g. of 85% potassium hydroxide. After stirring in the ice-bath for one hour the solution was saturated with potassium carbonate, extracted with chloroform, dried, and distilled at 178–179° (17 mm.); wt. 13 g.; m.p. 52–55°.

Anal. Calc'd for $C_{10}H_{10}N_2O_2$: C, 56.3; H, 8.9; N, 19.7.

Found: C, 56.7; H, 9.2; N, 20.0.

1,1'-Carbonyl-bis(4-methylpiperazine) dihydrochloride (XXVI). Phosgene was passed into a solution of 5 g. (0.005 mole) of 1-methylpiperazine, 2.8 g. of 85% potassium hydroxide, and 25 ml. of water until neutral, whereupon 2.8 g. more of potassium hydroxide was added and the procedure repeated until the solution was acid to Congo Red. The solution was then saturated with potassium carbonate and extracted with chloroform. The hydrochloride was formed by the introduction of dry hydrogen chloride and recrystallized from absolute alcohol, m.p. 303–304°; wt. 4.5 g.

Anal. Calc'd for $C_{11}H_{16}Cl_2N_4O$: C, 44.2; H, 7.4; N, 18.7.

Found: C, 44.2; H, 7.2; N, 19.2.

1-Phenylcarbonyl-4-methylpiperazine (XXIV). To a solution of 10 g. (0.1 mole) of 1-methylpiperazine in 50 ml. of dry benzene was added 10 g. (0.08 mole) of phenylisocyanate. The benzene was removed under suction and the crystalline residue recrystallized from benzene-petroleum ether, m.p. 126–130°, wt. 6.7 g.

Anal. Calc'd for $C_{13}H_{17}N_2O$: N, 19.1. Found: N, 19.1.

1-Diethylcarbamympiperazine (XII). A slurry of 696 g. (3.58 moles) of piperazine hexahydrate in 2190 g. of absolute ethanol was stirred at 50° until all of the piperazine had dissolved. While maintaining the temperature at 45–50° with an ice-bath, 485 g. (3.58 moles) of diethylcarbonyl chloride (8) was added in about twenty minutes.

The ice-bath was removed, and after stirring for one-half hour the reaction mixture was kept overnight at room temperature. The stirred reaction mixture was then made acidic to Congo Red with concentrated hydrochloric acid, while maintaining the temperature below 50°. After cooling to 20° the precipitated piperazine dihydrochloride was washed thoroughly with 95% alcohol. The yield of recovered piperazine dihydrochloride was 245 g., 43.0%.

The filtrate and washings from above were combined and concentrated on a steam-bath under reduced pressure to a volume of about 700 ml. To this thick syrup was added with stirring and cooling 50% sodium hydroxide solution until the reaction mixture was alkaline to phenolphthalein, and then solid sodium hydroxide was added with stirring and cooling until an oil separated. The slurry of salt and oil was filtered and the residue washed thoroughly with ether. The separated oil from the filtrate was combined with the ether washings and dried over solid sodium hydroxide. During this drying it was necessary to filter occasionally to remove precipitated salt. The ether was removed and the residue fractionated under reduced pressure. The fraction which boiled at 105–140° (corr.) at 3 mm. was redistilled and gave 266 g. of pure *1-diethylcarbamympiperazine*, which distilled at 113.5–115.5° (corr.) (3 mm.).

Anal. Calc'd for $C_8H_{12}N_2O$: C, 58.4; H, 10.3.

Found: C, 58.2; H, 10.6.

The residue from the refractionation gave 154 g. of *1,4-bis(diethylcarbamy)piperazine* which boiled at 174–178° (2 mm.). It melted at 55.7–56.0° (corr.) when recrystallized from mixed hexanes.

Anal. Calc'd for $C_{14}H_{28}N_4O_2$: C, 59.3; H, 9.9; N, 19.8.

Found: C, 59.2; H, 10.0; N, 19.9.

1-Diethylcarbonyl-4-carbethoxypiperazine (X). To 20 g. (0.13 mole) of 1-carbethoxypiperazine dissolved in 50 ml. chloroform was added slowly with stirring 8.5 g. (0.6 mole) of diethylcarbonyl chloride in 50 ml. of chloroform. From time to time more chloroform was added to maintain a clear solution. The reaction solution was then washed three times

with a saturated potassium carbonate solution and dried over magnesium sulfate and filtered. The chloroform was removed and the residue fractionated. The fraction boiling at 163–167° (3 mm.) was collected as the desired product, wt. 10.7 g.

Anal. Calc'd for $C_{12}H_{22}N_2O_2$: C, 56.0; H, 8.9; N, 16.3.

Found: C, 56.0; H, 9.4; N, 16.3.

1-Ethylcarbamy-4-methylpiperazine hydrochloride (XX). To 5 g. (0.05 mole) of 1-methylpiperazine in 25 ml. of chloroform was added 2.7 g. (0.025 mole) of ethylcarbamy chloride (9). The insoluble solids were dissolved in a small amount of water and extracted with ether after saturating the aqueous solution with potassium carbonate. The ethereal solution was dried with magnesium sulfate and the hydrochloride was precipitated as a solid with dry hydrogen chloride. It was recrystallized from alcohol-ether, m.p. 177°, wt. 1.7 g.

Anal. Calc'd for $C_8H_{12}ClN_2O$: N, 20.2. Found: N, 19.7.

1-Dialkylcarbamympiperazine (XIII). To a solution of 0.2 mole of piperazine in 100 ml. of alcohol was added with stirring 0.2 mole of dialkylcarbamy chloride (8, 10, 11, 12).¹ After standing overnight at room temperature the alcohol was removed and dilute hydrochloric acid was added to the residue. The 1,4-bis(dialkylcarbamy)piperazine was extracted with ether and the potassium carbonate saturated aqueous phase was extracted with chloroform to obtain the 1-dialkylcarbamympiperazine.

1-Diisopropylcarbamympiperazine (XIII). B.p. 146° (9 mm.).

Anal. Calc'd for $C_{11}H_{23}N_2O$: C, 62.0; H, 10.8.

Found: C, 61.6; H, 10.4.

1-Dimethylcarbamympiperazine (XI). B.p. 144–146° (15 mm.).

Anal. Calc'd for $C_7H_{15}N_2O$: C, 53.5; H, 9.5.

Found: C, 52.7; H, 9.6.

1-Dibutylcarbamympiperazine (XIV). B.p. 158–162° (5 mm.).

Anal. Calc'd for $C_{13}H_{27}N_2O$: N, 17.4. Found: N, 17.5.

1-Diisoamylcarbamympiperazine (XV). B.p. 200–202° (35 mm.).

Anal. Calc'd for $C_{15}H_{31}N_2O$: N, 15.6. Found: N, 15.5.

1-Diethylcarbamy-4-methylpiperazine (XXI). A. To 400 ml. of 90% formic acid was slowly added with stirring 580.5 g. (3.13 moles) of 1-diethylcarbamympiperazine or an equivalent of the hydrochloride salt. When the formic acid was added to the amine, a solid salt was formed. To this reaction mixture at 80° was slowly added 395 g. (4.74 moles; 50% excess) of 36% formalin, venting the evolved carbon dioxide through a reflux condenser. When the formaldehyde was added at room temperature and then heated, a sudden vigorous reaction took place at about 60°. Then after refluxing for one hour (105°) the mixture was distilled until the pot temperature reached 150°. The distillation residue was cooled to 30° and while stirring vigorously with strong cooling, 50% sodium hydroxide solution was slowly added until the reaction mixture was basic to phenolphthalein. The separated oil, after drying over solid sodium hydroxide, was distilled at 108.5–111° (corr.) (3 mm.); wt. 576 g., m.p. 47–49° (corr.).

B. To a cold solution of 1146 g. (6.0 moles) of 1-methylpiperazine dihydrochloride monohydrate in 1150 ml. of water was added with stirring and cooling 500 ml. of 50% sodium hydroxide solution to make the reaction mixture alkaline to Brilliant Yellow-red. While maintaining the temperature below 50°, 480 g. (12.0 moles) of sodium hydroxide pellets was dissolved while stirring and then with the temperature maintained at 35–40° with slight cooling 816 g. (6.0 moles) of diethylcarbamy chloride was added during the course of one-half hour. After an additional hour of stirring at this temperature the oil which separated was dried over potassium hydroxide pellets and distilled, wt. 778 g.

C. To a stirred solution of 10 g. (0.1 mole) of 1-methylpiperazine in 100 ml. of chloro-

¹ Prepared by the same procedure as described by Lumiere for analogous derivatives; b.p. 90–93° (15 mm.).

form there was added dropwise during one hour 6.1 g. (0.045 mole) of diethylcarbamyl chloride. After standing at room temperature for fifteen to twenty minutes, the clear solution was cooled in an ice-bath and treated with an excess of dry hydrogen chloride. The precipitated 1-methylpiperazine dihydrochloride was removed and the filtrate was evacuated to a solid on the water-pump. It was again taken up in chloroform, filtered, and re-evacuated to a solid; wt. 8.5 g., m.p. 150–153°. After recrystallization from anhydrous acetone it melted at 156.5–157° (corr.).

Anal. Calc'd for $C_{10}H_{22}ClN_2O$: C, 51.0; H, 9.4; N, 17.8; Cl, 15.0.

Found: C, 50.6; H, 9.4; N, 18.2; Cl, 15.2.

1-Dimethylcarbamyl-4-methylpiperazine hydrochloride (XIX). The same procedure was used as described for the diethyl analog of part C above. From 10 g. of 1-methylpiperazine was obtained 3.5 g. of compound which melted after recrystallization from alcohol-ether at 180–181°.

Anal. Calc'd for $C_8H_{18}ClN_2O$: C, 46.2; H, 8.7; N, 20.2.

Found: C, 46.8; H, 9.0; N, 20.9.

1-Diisopropylcarbamyl-4-methylpiperazine hydrochloride (XXII). This compound was prepared in the same manner as part C of the diethyl analog. From 5 g. of 1-methylpiperazine and 4.1 g. of diisopropylcarbamyl chloride was obtained 4.0 g. of the desired product. After recrystallization from chloroform-ethyl acetate it melted at 200–203°.

Anal. Calc'd for $C_{12}H_{26}ClN_2O$: C, 54.7; H, 9.1; N, 15.9.

Found: C, 55.2; H, 10.6; N, 15.0.

1-Dibutylcarbamyl-4-methylpiperazine hydrochloride (XXIII). This was prepared in the same manner as those described above. It was recrystallized from alcohol-ether, m.p. 151–152°.

Anal. Calc'd for $C_{14}H_{30}ClN_2O$: C, 57.6; H, 10.3.

Found: C, 57.8; H, 10.0.

1-Diethylcarbamyl-4-isopropylpiperazine hydrochloride (XXVIII). To an ice-cold solution of 20.1 g. (0.1 mole) of 1-isopropylpiperazine dihydrochloride (1), 6.6 g. of 85% potassium hydroxide, and 100 ml. of water was slowly added simultaneously 8.1 g. (0.055 mole) of diethylcarbamyl chloride and 6.6 g. of 8.5% potassium hydroxide dissolved in 10 ml. of water. After saturating with potassium carbonate and extracting with ether, the dried ethereal solution was treated with an excess of anhydrous hydrogen chloride. The precipitated solid was recrystallized from alcohol-ether and a small sample was sublimed at 150° (0.002 mm.), it melted with decomposition at 206–208°.

Anal. Calc'd for $C_{12}H_{26}ClN_2O$: C, 54.8; H, 9.4; N, 16.0.

Found: C, 54.8; H, 8.8; N, 15.9.

SUMMARY

1. A number of mono and disubstituted piperazines have been prepared and characterized.

2. 1-Diethylcarbamyl-4-methylpiperazine and 1-dimethylcarbamyl-4-methylpiperazine have pronounced anti-filarial activity.

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BOUND BROOK, N. J.

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A DRY SYNTHESIS OF AROMATIC SULFIDES: PHENYLENE SULFIDE RESINS

A. DOUGLAS MACALLUM

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Up to the present several of the simpler aromatic sulfide derivatives, such as phenyl sulfide, the disulfide, hexasulfide, and thianthrene, have been prepared directly from benzene by action of sulfur or sulfur chloride in the presence of aluminum chloride or iodine (1, 2). Other definitely oriented aromatic sulfides have been made from the corresponding sulfonates by roundabout methods (3) or through the hydrocarbon halides by way of the organometallic compounds (4).

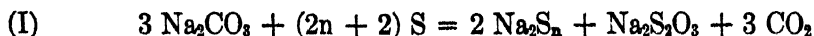
There are a number of rather labile haloaromatic compounds, such as chloronitronaphthalenes (5), chloronaphthols (6), or dibromoanthracene (7), which react easily enough with alcoholic solutions of the alkali metal sulfides and polysulfides. However, this is exceptional and most aromatic chloro compounds, including the chlorobenzenes, are comparatively inert, and have been made to react with alkali sulfides and polysulfides only in the presence of water at high pressures, and temperatures of 300–350° (8, 9).

The technique of preparing aromatic sulfide and polysulfide derivatives has been much simplified by the method described here, which hinges on an observation that aromatic chloro compounds, though generally unaffected by dry metal sulfides, can be made to react with them in a dry way by the addition of quite small amounts of free sulfur. The reaction goes under pressure in the liquid-solid phases at temperatures of 275–360°, best at about 300°.

By a further simplification, which gives satisfactory results in many cases, the metal sulfides are not used as such, the chloro hydrocarbons being reacted with nascent metal sulfide as it is formed under the above conditions from mixtures of sulfur with a number of oxides, carbonates, or borates of the alkali or alkaline earth metals.

The two methods are of use in preparing simple bicyclic sulfides, such as phenyl sulfide or thianthrene, or aromatic sulfide polymers, such as the phenylene sulfide resins dealt with in this paper. These dry methods decrease considerably the difficulties due to corrosion and pressure, as well as to side reactions involving hydrolysis or reduction, which are encountered when the reactions are carried out in the presence of water.

The formation of alkali metal sulfides and polysulfides from the alkali carbonates and sulfur has been studied by Pearson and Robinson (10), the reaction being reported as going slowly at 200°, but with increasing speed at higher temperatures. At 350° the reaction followed mainly equation (I), at 640° mainly equation (II), some sulfite being produced along with the sulfate formed.



Actually, however, when such a mixture, in some excess, is heated at 300–340° with *p*-dichlorobenzene in order to produce a sulfide derivative, the soluble by-products are found to include both thiosulfate and sulfate. It would thus appear that the formation of a polyphenylene sulfide resin, which is obtained under the above conditions, involves at least two reactions (equations III and IV).

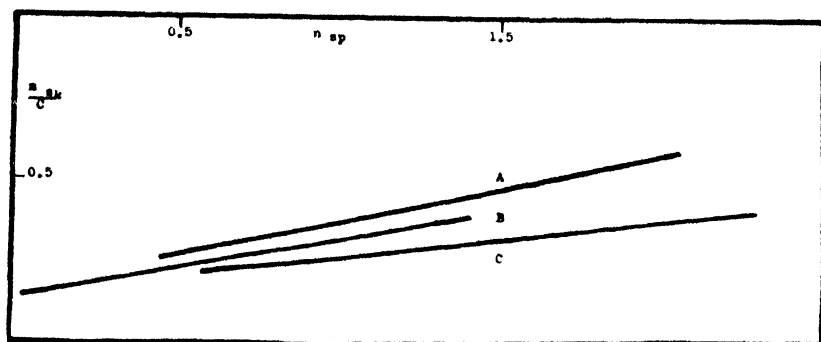
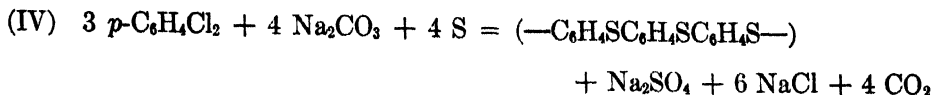
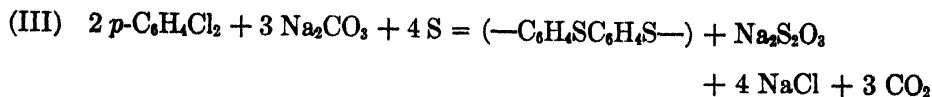


FIG. 1. Showing curves based on specific viscosity data for several *p*-phenylene polysulfide polymer resins in sulfur at 132° (over boiling chlorobenzene). The polymers were obtained from *p*-dichlorobenzene by reaction with mixtures of anhydrous sodium carbonate and sulfur as described in the text. The curves A, B, and C are for resins of 47.8, 56.2, and 68.2% sulfur respectively. The monosulfide resins, containing about 30% sulfur, are too sparingly soluble to affect the viscosity of sulfur appreciably at 132°. The concentrations here have been in terms of g. resin per 100 cc. sulfur solution at 132°.

From the curves, the intrinsic viscosities of the resins are figured at about 0.15 by the method of Huggins, *Ind. Eng. Chem.*, **35**, 980 (1943).

One high-molecular form of *p*-phenylene disulfide, ($\text{C}_6\text{H}_4\text{S}_2$), was obtained by Leuckart (11) and by Parekh and Guha (3) through the chemical oxidation of dithiohydroquinone. This substance has been described as an amorphous powder, insoluble in all common solvents and not melting at 300°. However, products of this type, prepared by the methods described here using mixtures of *p*-dichlorobenzene with sulfur and sodium carbonate, are quite different in physical properties. They are all either fusible or thermoplastic, the di- and poly-sulfide compounds dissolving in molten sulfur and having an intrinsic viscosity in the neighborhood of 0.15 in this solvent (Figure 1). Molecular weights on these compounds are difficult to determine by conventional methods owing to a dearth of suitable solvents. However, some initial data, obtained by isothermal distillation of the sulfur solutions, would indicate a probable weight figure in excess of 9000 (Table I).

When the resins are purified and subjected to thorough elementary analysis, they correspond closely to an empirical composition of $(C_6H_4S_x)$, where x stands for one or more atoms of sulfur. They are practically insoluble in sodium sulfide solutions and have so far exhibited no dyeing properties. They would thus differ, in properties as well as in composition, from the sulfur dyes having an empirical composition of (C_6HS_2) or $(C_6H_2S_4)$, which have been obtained in the dehydrogenation of gaseous benzene or toluene by means of sulfur at ordinary pressure and at elevated temperatures, generally in excess of 360° (12).

Much of the experimental work on this subject has been carried out using stationary charges heated in sealed glass pressure tubes. However, for the preparation of plastic resins, having regard for the viscous nature of the mixtures during the reaction, more uniform products are to be obtained where the charges are steadily rotated during the heating. In this way, and by a proportioning of the mixtures and control of the temperature at close to 300° , it has been possible to build up phenylene sulfide polymers of considerably improved toughness and strength. The flexural and tensile strengths of these resins, which can run at 5000–7000 lb. per sq. in. in the unplasticized state, would be in agreement with a reasonably high degree of polymerization, maybe 100–200, if analogy with cellulose derivatives is to be accepted in this respect (15).

Otherwise the phenylene sulfide resins obtained by the present method can be described as light colored, cream to canary yellow in the powder state, and as having a high thermal stability. Their chemical stability is generally high also, except toward strong oxidizing agents, such as nitric acid. After fusing or pressing, they take on the character of glasses, but with rise in temperature become resilient and finally pass into a plastic state. Some of the resins exist in a tough but vitreous or resilient condition over a wide temperature range. When plasticized by sulfur, the phenylene di- and poly-sulfide resins are mostly rubber-like in properties; they also readily dissolve on heating with organic disulfides, such as phenyl disulfide or tetramethylthiuram disulfide, but evidently undergo a disproportionation in doing so, causing little change in viscosity but a large depression of the freezing point of the solvent.

The tendency toward formation of plastic sulfide resins is not confined to the metathesis reactions of *p*-dichlorobenzene but has been observed as well with *m*-dichlorobenzene, with mixed dichlorobenzenes and other dihalogenated aromatic compounds, including diphenyl, diphenyl ether, terphenyl, and naphthalene derivatives. The resins are generally sparingly soluble in organic solvents except where the reaction mixtures started with include some monochloride along with the dichloride. Such mixtures tend to yield low-melting, soluble resins of low viscosity and molecular weight.

Polychlorinated benzenes, such as 1,2,4-trichlorobenzene, 1,2,4,5-tetrachlorobenzene, or hexachlorobenzene, react under like conditions but lead to practically insoluble, yellow to green pigments, which do not fuse at temperatures up to 450° . They do not seem to have any dyeing effects.

TABLE I

SHOWING MOLECULAR WEIGHT DATA ON A RELATIVELY HIGH-MOLECULAR *p*-PHENYLENE POLYSULFIDE RESIN (H) AS DETERMINED BY ISOTHERMAL DISTILLATION IN SULFUR AT 295–305° IN BALANCE WITH A SIMILAR MIXED SULFIDE RESIN (L) OF KNOWN MOLECULAR WEIGHT

RESIN	WT. G.	SOL'N., G.	MOLES/KG.	WT. CHANGE, G.	M. WT.
L	0.0695	1.1505	0.04	+0.009	1500
H	.377	1.0425	below	– .0145	above 9000
L	.0286	0.978	0.0195	– .038	1500
H	.0985	.29	above	+ .0375	below 17,000

The resin (H) had a sulfur content of 47.8% and was obtained from *p*-dichlorobenzene by reaction with a mixture of anhydrous sodium carbonate and sulfur at 300–340°. It was sealed up, after evacuating, in one arm of an inverted "Y"-tube in balance with a low-molecular, carbon disulfide-soluble resin (L) obtained similarly, starting with a mixture of monochloro- and *p*-dichloro-benzene, as described in the last example in the text. Before use, both resins were freed as far as possible of volatile materials by prolonged vacuum-distillation at 300–340° in sealed tubular stills.

TABLE II

SHOWING RECOVERY BALANCE OF SOLUBLE BYPRODUCTS WHEN 3.3 G. OF *p*-DICHLORO-BENZENE WAS HEATED FOR 20 HOURS AT 300–340° WITH 3.9 G. OF SODIUM CARBONATE AND 3 G. OF SULFUR

The procedure of Shereshevskii (13) and Paessler (14) for analysis of inorganic sulfide mixtures was followed here for the most part.

BY-PRODUCT	ANALYSIS YIELD, G.	RECOVERY % ON	
		Na ₂ CO ₃	<i>p</i> -C ₆ H ₄ Cl ₂
Na ₂ S.....	0.0214	0.7	—
Na ₂ S ₂ O ₃75	12.8	—
Na ₂ SO ₄442	8.4	—
Na ₂ CO ₃553	14.1	—
NaCl.....	2.495	58.0	95.1

The aqueous extracts from the phenylene polysulfide resin were here diluted to a fixed volume, 125 cc., and 5- or 10-cc. samples used for the different analyses. Thiosulfate was determined by iodine titration after precipitating sulfide and polysulfide with zinc sulfate; sulfide and thiosulfate together by treatment with excess acid iodine solution; carbonate and sulfide together by acid titration with phenolphthalein as indicator; sulfate by boiling with dilute hydrochloric acid to eliminate sulfur dioxide, filtering from liberated sulfur and treating with barium chloride; chloride by evaporating over steam in a crucible, burning the residue with a 1:3 mixture of potassium nitrate and sodium carbonate, then working up for chloride in the usual way, acidifying with nitric acid and treating with silver nitrate; total extracted salts by fuming down several times with excess sulfuric acid and weighing as sodium sulfate.

The sulfur liberated in the sulfate determination corresponded to an analysis yield of 0.16 g. as against 0.1519 g. calc'd for the Na₂S₂O₃ found; the extracted salts, converted to sulfate, were equivalent to 5.0882 g. Na₂SO₄ or a 97.3% recovery on the Na₂CO₃ used.

EXPERIMENTAL

Thianthrene. A mixture of 4 g. of dry, U.S.P. calcium sulfide (63.7% sulfide conc'n), 0.283 g. of sulfur, and 4 g. of *o*-dichlorobenzene, is sealed up in a glass tube at about 25 mm. pressure and heated undisturbed for about 20 hours at 300–340°. (Ordinary Pyrex tubes of 14–15 mm. diameter and 14–16 inches long serve well enough here if heated within a capped steel nipple or pipe, perforated by a few touch-holes.) The product is isolated by direct distillation at about 250° (25 mm.) or by extraction with hot benzene. It is purified by redistilling over about half its weight of copper powder. It comprises colorless crystals of thianthrene; m.p. 158.8–159°. The yield is 75% or more on the dichlorobenzene.

Anal. Calc'd for $C_{12}H_8S_2$: S, 29.6; mol. wt. 216.

Found: S (Asbóth method), 29.0; mol. wt. (Rast), 207–214.

When dry calcium sulfide is heated under the same conditions with *o*-dichlorobenzene alone, no separable thianthrene is formed, the starting materials being recovered practically unchanged.

Phenyl sulfide and disulfide. A mixture of 2.5 g. of calcium oxide powder (calcined slaked lime), 1.43 g. of sulfur, and 4.52 g. of chlorobenzene, is sealed up in an evacuated tube and heated 20 hours at 295–305°. The product can be isolated from the mixture by direct distillation under reduced pressure, or by extraction with carbon tetrachloride. It comprises a mixture of phenyl sulfide and disulfide boiling at 290–315°, the yield being 75% or more on the chlorobenzene. Redistilled over copper powder, the phenyl sulfide boils at 290–296° and has a specific gravity of 1.118 at 16°.

Phenylene sulfide polymers. A mixture of 3 g. of sulfur, 3.9 g. of low-density sodium carbonate (obtained by heating sodium bicarbonate at 250–300°) is pulverized together and added to 3.3 g. of *p*-dichlorobenzene. After evacuating and sealing, the tube is heated 20 hours at 300–340° in a nearly horizontal position. The reaction develops a high pressure, the effluent gases, on cautious opening of the tube, being practically odorless. After pulverizing, extracting with water, and drying, the crude product, 4.1 g., is a sulfur-colored resin containing 56.2% total S (by modified Liebig method), 9–10% labile S [by Parker's method (16) modified by carrying out in presence of toluene].

The crude material is purified for analysis by continuous extraction with acetone and toluene in succession and dried at 140–150° under reduced pressure. The purified resin is 50–51% of the crude. It is straw-colored and brittle cold, resilient at 80–180°, plastic from this temperature up to above 350°. It corresponds in empirical composition to $(C_6H_4S_2)_x$.

Anal. Calc'd: C, 48.1; H, 2.67; S, 49.2.

Found: C(micro), 47.9–48.1; H(micro), 2.5–2.7; S(total), 48.2–48.6; also 1–2% labile S; 0.3% ash; less than 0.4% Cl.

The reaction by-products here comprised mainly sodium chloride along with lesser amounts of thiosulfate, sulfate, and unchanged sodium carbonate, very little unreacted sodium sulfide (Table II).

When *p*-dichlorobenzene has been heated with either sodium carbonate or sulfur alone under the above conditions, practically no inorganic chloride or resin has been obtained.

A resin approaching in composition a phenylene monosulfide polymer is obtained as follows: A mixture of 1.2 g. of sulfur, 4 g. of anhydrous sodium carbonate, and 3.3 g. of *p*-dichlorobenzene is heated as above, giving 2.4 g. of pale yellow crude resin, which is purified by continuous extraction in the same way. After drying, the recovery amounts to 87–88% of the crude. It comprises a white powder, brittle cold, fusing fairly sharply at 255°. The analysis corresponds to an empirical composition of $(C_6H_4S_{1.2})_x$.

Anal. Calc'd: C, 62.9; H, 3.5; S, 33.6.

Found: C, 62.7–62.9; H, 3.4–3.5; S, 30.8–30.9; ash, 0.4; Cl, 0.8.

(The figures for carbon and hydrogen quoted above were obtained in the laboratory of Dr. C. Tiedcke in New York.)

The physical character of such a resin can be much improved by closer control of the reaction conditions. Thus when such a mixture as the last is rotated continuously during

the heating and the temperature kept at 300°, the resin obtained molds very well between aluminum plates at 260–280°, forming tough, glassy sheets which become resilient from the softening point, about 100°, to about 210°, when the material becomes workable. The resins obtained in this manner show the most promise as regards physical strength. The toughness can be still further increased by use of somewhat less sulfur in the reaction mixtures. However, inclusion of even small amounts of water in the mixtures has been observed to lower the strength of the resins obtained.

Soluble mixed sulfide resin. A mixture of 3 g. of sulfur, 3.9 g. of anhydrous sodium carbonate, 3 g. of *p*-dichlorobenzene, and 0.5 g. of chlorobenzene, is heated 20 hours in a sealed, evacuated tube at 300–325°, and the cooled mixture extracted with water after releasing the gas generated in the reaction. The dried product, 4.3 g., contains 54.8% S and is a yellow, brittle resin, softening at 30°, becoming moderately fluid at 70°. It is easily soluble in carbon disulfide and is recovered by evaporating the solvent (finally at 140–180° under reduced pressure) as a clear, yellow, low-melting glass. The molecular weight is about 1500 (1480 found in balance with olein by the Barger method).

SUMMARY

A convenient process has been devised for preparing aromatic sulfide and polysulfide compounds in a dry way by heating the aromatic chloro compounds with certain metal sulfides in presence of some free sulfur. Mixtures of sulfur with a number of oxides or salts of metals of groups I and II of the periodic table can also be substituted for the preformed metal sulfides.

By this method the aromatic dichloro compounds give condensation products, mostly in the form of sparingly soluble, high-melting, plastic resins, some of moderately high apparent molecular weight. The physical strength of some of the resins is satisfactory. Mixed sulfide resins which are both soluble and low-melting can also be made this way.

LONDON, ONTARIO, CANADA

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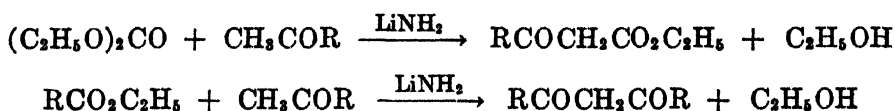
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CONDENSATIONS EFFECTED BY THE ALKALI AMIDES. I. THE USE OF LITHIUM AMIDE IN THE SYNTHESIS OF CERTAIN β -KETO ESTERS AND SYMMETRICAL β -DIKETONES¹

GLENN R. ZELLARS AND ROBERT LEVINE

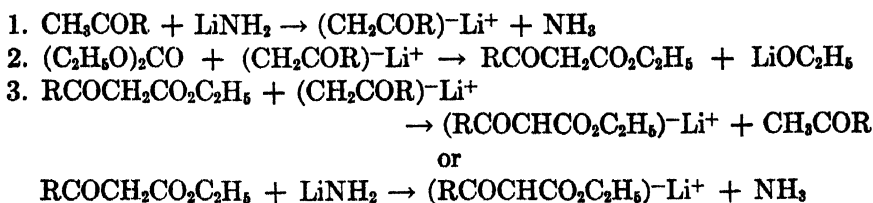
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The carbethoxylation of methyl ketones with diethyl carbonate to form β -keto esters has been effected previously by means of sodium ethoxide (1), sodium triphenylmethide (2), or sodium amide (3); and the acylation of ketones with ordinary esters has been effected by means of sodium metal (4), sodium ethoxide (5), sodium triphenylmethide (6), or sodium amide (6, 7). In the present investigation, these two types of condensations have been effected by lithium amide. The reactions may be illustrated by the following equations:



The method of carbethoxylation consists of adding the ketone to an ethereal suspension of lithium amide and refluxing the ethereal suspension of the lithium derivative of the ketone with diethyl carbonate. As was previously observed by Levine and Hauser (3), the presence of excess alkali amide increases the yield of β -keto ester appreciably. To see what effect the amount of lithium amide had on the yield of β -keto ester, the carbethoxylation of methyl isobutyl ketone was carried out with molecular equivalents of lithium amide and ketone and also with two equivalents of base to one of the ketone. The yield of β -keto ester using molecular equivalents of lithium amide and methyl isobutyl ketone was 39%. However, when two equivalents of base to one of ketone were used, the yield of product was 62%.

The following mechanism indicates how the presence of excess base might increase the yield of β -keto ester.



In the first step the ketone is converted completely to its lithium derivative by one equivalent of lithium amide. In the second step the lithioketone condenses with diethyl carbonate. One-half of the ketone could be regenerated in

¹ This work is based in part on a thesis to be submitted by Glenn R. Zellars in partial fulfillment of the requirements for the degree of Master of Science at the University of Pittsburgh.

the third step, thus making the maximum yield of the β -keto ester 50%. However, if two equivalents of lithium amide are used to one of the ketone, the third step of the reaction will be effected by the strongest base present (*i.e.*, the lithium amide) and the yield of the product may be theoretically 100%. In Table I are found the yields and boiling points of the β -keto esters which were prepared. It may be seen that these compounds have been prepared in fair

TABLE I
 β -Keto Esters

KETONE	β -KETO ESTER	B.P.		YIELD, %	COPPER SALT M.P. (UNCOR.), °C
		°C	MM.		
Methyl <i>n</i> -propyl	Ethyl <i>n</i> -butyrylacetate	90-93	14	26	122-123 (8)
Methyl isobutyl	Ethyl isovalerylacetate	92-94	13	62	121.7-122 (9)
2-Acetylthiophene	Ethyl β -keto- β -(2-thienyl)propionate ^a	149-152	6	41	—
Acetophenone	Ethyl benzoylacetate	135-140	6	50	179-180 (10)

^a 1-Phenyl-3-(α -thienyl)-pyrazolone-5, m.p. 135.2°. See ref. (3)

TABLE II
 β -Diketones

KETONE	ETHYL ESTER	PRODUCT	B.P.		YIELD, %	COPPER SALT M.P. (UNCOR.), °C
			°C	MM.		
Acetone	Acetate	Acetylacetone	139-141	757	50	decomp. (11)
Methyl ethyl	Propionate	Dipropionylmethane ^a	78-81	30	51	209-210 (12)
Methyl <i>n</i> -propyl	<i>n</i> -Butyrate	Di- <i>n</i> -butyrylmethane	101-102	20	76	156-157 (14)
Methyl isobutyl	Isovalerate	Diisovalerylmethane	114-116	20	75	157-158 (7)
Methyl <i>n</i> -amyl	Caproate	Dicaproylmethane	162-165	20	65	119-120 (7)
Acetophenone	Benzoate	Dibenzoylmethane ^b	77-78 (m.p.)		71	—

^a The washings and filtrate from this copper salt were treated with 10% sulfuric acid and extracted with ether. After distilling off the solvent, there was obtained 11% of methyl propionylacetone, b.p. 93-99° at 30 mm; m.p. of copper salt 176-177.5°. See ref. (13).

^b See ref. (15).

to good yields. These yields compare favorably with those obtained using sodium amide (3).

The method of acylation consists of adding the ketone to a stirred ethereal suspension of lithium amide and refluxing the ethereal suspension of the lithio-ketone with the appropriate ester. As observed above in the preparation of β -keto esters, the use of two equivalents of lithium amide to one of ketone increased the yields appreciably. In Table II are given the yields and boiling

points of the β -diketones prepared. In the acylation of methyl ethyl ketone with ethyl propionate, 11% of methyl propionylacetone (formed by acylation at the methylene carbon atom) was obtained in addition to the much higher yield of the methyl derivative. The production of both methyl and methylene derivatives in the acylation of ketones with esters has been observed earlier when sodium amide was used as the condensing base (6, 7).

EXPERIMENTAL²

Preparation of lithium derivatives of ketones. The apparatus used in these reactions consisted of a 500-cc. three-necked round-bottomed flask equipped with ground-glass joints, a mercury-sealed stirrer, a reflux condenser, and an addition funnel (protected from atmospheric moisture by a drying tube filled with Drierite). The reaction was carried out in a well-ventilated hood. Four-tenths of a mole (9.2 g.) of lithium amide was placed in the flask and covered with 100 cc. of absolute ether. The stirrer was started and 0.2 mole of the appropriate ketone, dissolved in 50 cc. of absolute ether, was added at such a rate as to keep the ether gently refluxing. If the refluxing became too violent, the reaction mixture was cooled with an ice-bath. After the addition of the ketone was complete (about 15 minutes), the reaction mixture was stirred for thirty minutes longer.

Condensation of lithio-ketones with esters. To the rapidly stirred suspension of the lithio-ketone, 0.4 mole of the required ester, dissolved in 50 cc. of absolute ether, was added. The reaction mixture was then stirred and refluxed for two hours on a water-bath.

The isolation of β -keto esters. The contents of the flask were poured onto a mixture of crushed ice and 125 cc. of concentrated hydrochloric acid. The two phases were separated and the aqueous phase was then extracted with several 100-cc. portions of ether. The ethereal phases were combined, dried over Drierite, and the ether distilled. The residue was first distilled at atmospheric pressure to remove the ketone and most of the excess diethyl carbonate and then *in vacuo* to obtain the β -keto ester. The yields of these compounds are given in Table I.

The isolation of β -diketones. The reaction mixtures were decomposed as described above for the β -keto esters. After distilling off the ether, the residue was dissolved in an equal volume of methanol and then poured into 350 cc. of a hot saturated solution of copper acetate. The copper salts of the β -diketones usually separated out as blue solids. The flask containing the copper salt was placed in a refrigerator over night to allow the precipitation of the salt to become complete. The copper salts were then filtered and washed with ice-cold low-boiling petroleum ether until the washings were practically colorless. The crude copper salt was poured into a separatory funnel and shaken with 10% sulfuric acid and ether until decomposition of the copper chelate was complete and two homogeneous phases were present. The phases were separated and the ethereal solution was dried over Drierite. The ether was distilled off at atmospheric pressure and the residue distilled *in vacuo*. The yields of the β -diketones are given in Table II.

SUMMARY

Various ketones have been carbethoxylated with diethyl carbonate in the presence of lithium amide to give β -keto esters in fair to good yields.

Certain ketones have been acylated with aliphatic and aromatic esters to produce symmetrical β -diketones in good yields.

As previously observed with sodium amide (7), the acylation of methyl ethyl

² The lithium amide used in this investigation was purchased from the A. D. Mackay Company of New York.

ketone with ethyl propionate in the presence of lithium amide produces both methyl and methylene derivatives.

PITTSBURGH 13, PA. •

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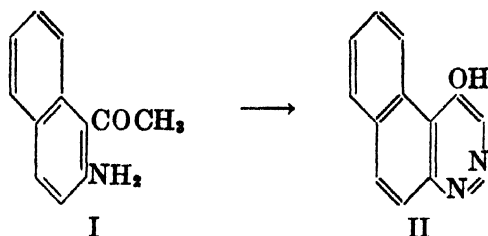
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PRODUCTS OF FRIEDEL-CRAFTS ACYLATION OF β -SUBSTITUTED NAPHTHALENES

NELSON J. LEONARD AND ARCHIBALD M. HYSON

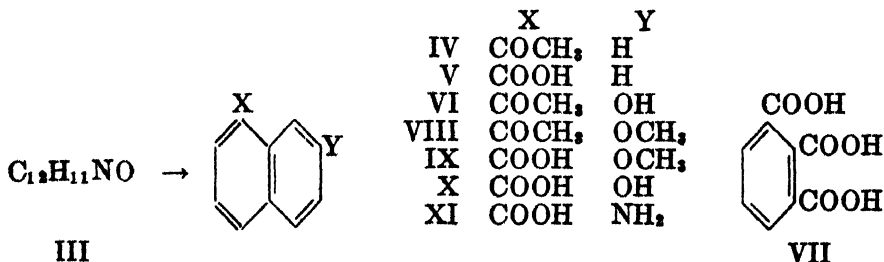
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The diazotization and subsequent cyclization of *o*-aminoaryl alkyl ketones with the formation of 4-hydroxycinnolines is of such generality (1, 2, 3) as to serve as a positive indication of the vicinal arrangement of the amino and acyl groups on the aromatic nucleus in such compounds. When it was discovered (4) that the compound reported to have the structure 2-amino-1-acetonaphthone (I) (5) did not form a 4-hydroxycinnoline (II) under the usual diazotization and cyclization conditions, there was reasonable doubt as to the validity of the assigned structure of this aminoacetonaphthone. The compound (III), which had been



obtained by Friedel-Crafts acetylation of acet-2-naphthalide followed by hydrolysis (2, 5), was therefore subjected to degradative study to determine the position at which the acetyl group had entered the molecule.

Removal of the amino group of III by diazotization and subsequent treatment with hypophosphorous acid led to the formation of 1-acetonaphthone (IV), which was identified by the melting point of its picrate and by the melting point of the 1-naphthoic acid (V) formed by hypochlorite oxidation. The attachment of the acetyl group at an *alpha* position was thus indicated. Replacement of the amino group of III by a hydroxyl group gave a hydroxyacetonaphthone (VI) (4) which was oxidized by permanganate to hemimellitic acid (VII). With the



position of attachment of the acetyl group thus limited to the 5- or the 8-position relative to the 2-amino group in III, the final distinction was possible through recourse to mild oxidation reactions. Conversion of VI to the methoxyaceto-

naphthone VIII was followed by hypochlorite oxidation to the known 7-methoxy-1-naphthoic acid (IX) (6), and the acid hydrolysis product of IX was identified as 7-hydroxy-1-naphthoic acid (X) (6, 7). The product of hypiodite oxidation of the acetyl derivative of III was identified as 7-acetylamino-1-naphthoic acid and was hydrolyzed to the known 7-amino-1-naphthoic acid (XI) (8).

The accumulation of corroborative evidence for 7-amino-1-acetonaphthone as the structure of III was considered desirable because this conclusion makes necessary the revision of the structures of numerous related naphthalene derivatives described in the literature as 1,2-substituted compounds.

The evidence that the "2-amino-1-acetonaphthone" of Brown, Jacobs, Winstein, Levy, Moss, and Ott (5), obtained by Friedel-Crafts acetylation of acet-2-naphthalide followed by hydrolysis, is in reality 7-amino-1-acetonaphthone suggests that the derived "2-halo-1-acetonaphthones" are likewise 1,7-isomers. These workers (5) prepared a bromoacetonaphthone from III by diazotization followed by a Sandmeyer reaction. The compound obtained was found to be identical with one of the bromoacetonaphthones prepared by Friedel-Crafts acetylation of 2-bromonaphthalene and previously assigned the structure 2-bromo-1-acetonaphthone (9).

Dziewonski and Sternbach (9) converted their 2-bromoacetonaphthone to the oxime and thence by a Beckmann rearrangement to a 2-bromoacetonaphthalide. Hydrolysis gave a 2-bromonaphthylamine, the benzoyl derivative of which melted at 220°. More recently, 2-bromo-1-naphthylamine was prepared from 1-nitro-2-naphthylamine (10) and the melting point of the benzoyl derivative was found to be 179°. Hence, the 2-bromonaphthylamine of Dziewonski and Sternbach could not be 2-bromo-1-naphthylamine and, in turn, their 2-bromoacetonaphthone could not be 2-bromo-1-acetonaphthone.

The same 2-bromoacetonaphthone was converted by nitric acid oxidation to a 2-bromonaphthoic acid, m.p. 233° (9). Prior to the work of Dziewonski and Sternbach, neither 2-bromo-1-naphthoic acid nor 7-bromo-1-naphthoic acid had been described in the literature. However, in 1938 Goldstein and Fischer (11) prepared 7-bromo-1-naphthoic acid and reported the melting point 237° (cor.). The proximity of melting points is suggestive of identity inasmuch as in the chloro series 7-chloro-1-naphthoic acid melts at 243° (11) and 2-chloro-1-naphthoic acid melts at 153° (12). A similar disparity would also be expected with the corresponding bromonaphthoic acids, which indicates that the bromonaphthoic acid obtained by Dziewonski and Sternbach is not 2-bromo-1-naphthoic acid but more likely 7-bromo-1-naphthoic acid. The synthesis of the 1,2-acid by an unequivocal method would eliminate any doubt.

Dziewonski and Sternbach (9) also converted their 2-bromonaphthylamine to a dibromonaphthalene, m.p. 68°, and reported this compound to be identical with a dibromonaphthalene described by Guareschi (13). Meldola (14) prepared 1,2-dibromonaphthalene and originally reported the melting point 63°. Further purification was found to raise the melting point to 67–68° (15). 1,7-Dibromonaphthalene is reported to melt at 74° (16) and 75° (17). It is possible that the melting point (68°) of the dibromonaphthalene prepared by Dziewonski and

Sternbach could likewise be revised upward to correspond to the melting point of the 1,7-compound, with which it should be identical on the basis of all other evidence presented. According to Armstrong and Rossiter (16), little or no reliance can be placed on either the appearance or melting point of the dibromonaphthalenes, as a slight impurity suffices to produce very misleading changes.

In Table I are assembled and compared the melting points of authentic 1,7-compounds, of corresponding authentic 1,2-compounds, and of those supposedly "1,2-compounds" which now must be regarded as 1,7.

Applying these findings to correction of the literature, the 2-amino-1-acetonaphthone (2) and hydroxyacetophenone (4) of Leonard and Boyd become 7-amino-1-acetonaphthone and 7-hydroxy-1-acetonaphthone, respectively. All of the naphthalene compounds described by Brown, Jacobs, Winstein, Levy, Moss and Ott (5) as "1,2-compounds" are actually 1,7-compounds; these include the substituted acetophenones, the derived ω -bromoacetophenones, bromohydrins, dialkylammonium bromides, and the final dialkylamino alcohols

TABLE I
COMPARISON OF 1,7- AND 1,2-NAPHTHALENE DERIVATIVES

MELTING POINTS, °C

Authentic 1,7-Compound	"1,2-Compd."	1,2-Compd.
7-Bromo-1-naphthylamine, N-benzoyl.	220	179
7-Bromo-1-naphthoic Acid, 237	233	
7-Chloro-1-naphthoic Acid, 243		153
1,7-Dibromonaphthalene $\left\{ \begin{array}{l} \text{(a)} \\ \text{(b) 74, 75} \end{array} \right.$	68	63 67, 68

(a) First report, (b) Report following further purification.

which were tested for antimalarial activity. The 2-bromo-1-acetonaphthone of Dziewonski and Sternbach (9) is actually 7-bromo-1-acetonaphthone and all of the compounds derived from this bromo ketone (9) must now be regarded as 1,7-compounds. Revision of structure is also necessary for two compounds obtained by Anderson and Johnston (18) from the 2-bromo-1-acetonaphthone of Dziewonski and Sternbach: 1-(2-bromonaphthyl)diphenylchloromethane is, instead, 1-(7-bromonaphthyl)diphenylchloromethane, and 1-(2-bromonaphthyl)diphenylcarbinol is 1-(7-bromonaphthyl)diphenylcarbinol.

In the Friedel-Crafts acylation of naphthalenes substituted in the β -position by halogen or acetylamino we have shown that substitution occurs preferentially in the unsubstituted ring. This orientation may be due to the deactivation of the substituted ring toward electrophilic substitution. Such deactivation would be due to the halogen atom in the 2-halonaphthalenes and to aluminum chloride complex formation by the 2-acetylamino group in acet-2-naphthalide. Two factors influence the position in the unsubstituted ring at which acylation will then occur. One is the orientation effect of the 2-halo or acetylamino group, which will favor substitution in the 6- or 8-position. The other is the usual

α -orientation effect of the naphthalene nucleus, which will encourage substitution in the 5- or 8-position. The two effects supplement each other in directing substitution at the 8-position, which explains the formation of the 2,8 (or 1,7)-disubstituted naphthalenes in preponderant yield in the acylation of these β -substituted naphthalenes. It is interesting and not altogether consistent with these observations that the 1-halonaphthalenes undergo Friedel-Crafts acylation predominantly in the 4-position. Yet there appears to be no question as to the established structure of these 1,4-compounds (19).

In the Friedel-Crafts acylation of naphthalenes substituted in the β -position by methoxyl, the products obtained are more diverse, and the orientation effect of the methoxyl group appears to be more important than any aluminum chloride-complexing effect in deciding the position of substitution. One complicating factor in the study has been the cleavage by aluminum chloride of the ether linkage in the β -alkoxynaphthalenes (20). With a monofunctional acylating agent, substitution on 2-methoxynaphthalene occurred at the 1-position (21, 22, 23). With a bifunctional acylating agent such as oxalyl chloride or malonylchloride, substitution occurred at both 1- and 8-positions relative to the 2-methoxyl group (24, 25, 26). Finally, there is conflicting evidence in the literature as to the structure of the compound produced in the reaction of 2-methoxynaphthalene in carbon disulfide with succinic anhydride in the presence of aluminum chloride. One group of investigators (27) indicated the 8-position, and another group (28) the 1-position as the point of substitution on the naphthalene nucleus, with no plausible explanation being advanced for these differing products.

EXPERIMENTAL¹

Acet-2-naphthalide, m p. 131–132°, was prepared by the method of Kaufman (29).

7-Amino-1-acetonaphthone, m p. 108.5–110°, was prepared by Friedel-Crafts acetylation of acet-2-naphthalide according to the method of Brown and co-workers (5) and reported as 2-amino-1-acetonaphthone.

1-Acetonaphthone. Two grams of 7-amino-1-acetonaphthone was diazotized in the usual manner (4) and fifteen mole-equivalents of hypophosphorous acid was added to the cold solution during fifteen minutes. The reaction mixture was maintained at 0° for 24 hours, and the reddish brown oil which separated was extracted with ether. The ether solution was washed with 5 *N* sodium hydroxide, with water, and dried. An oil remained after the ether was evaporated.

The picrate was prepared by treating a small amount of the oil with picric acid in ether and was recrystallized from ether; m.p. 115.5°. Stobbe (30) reported the melting point 116°.

1-Naphthoic acid. About 0.3 g. of 1-acetonaphthone in aqueous methanol was treated with a solution of sodium hypochlorite (commercial Clorox) and the reaction mixture was worked up in the usual manner for hypochlorite oxidations. After purification, the acid obtained melted at 161°, and a mixed melting point with an authentic sample of 1-naphthoic acid showed no depression.

7-Hydroxy-1-acetonaphthone. The diazotization of 9.2 g. (0.05 mole) of 7-amino-1-acetonaphthone was carried out in the usual manner (4), and the solution was allowed to stand for two days at room temperature before heating on the steam-bath for one hour. Sufficient ethanol was added to dissolve the black precipitate, and the solution was filtered hot. The

¹ All melting points are corrected. Microanalyses by Miss Theta Spoor.

cooled filtrate was extracted with ether and the combined ether extracts were evaporated. The residue was dissolved in benzene, and the solution was filtered following decolorization with Darco. The crystals which formed when the filtrate was cooled were recrystallized from benzene-ligroin as pale yellow needles, m.p. 149–150°.

Hemimellitic acid (51). One gram of 7-hydroxy-1-acetonaphthone was subjected to vigorous alkaline permanganate oxidation followed by a short period of acidic oxidation. After removal of the precipitated manganese dioxide, the solution was evaporated nearly to dryness and 50 ml. of 12 *N* hydrochloric acid was added to the sludge. This mixture was extracted repeatedly with ether and ethyl acetate, and the combined extracts were evaporated to dryness. The residue was dissolved in a few ml. of hot water, decolorized with Darco, and filtered. An equal quantity of 12 *N* hydrochloric acid was added to the filtrate and the resulting yellow-green solution was placed in the ice-box overnight. Small white crystals appeared which melted at 184–197°. The material was dissolved in a small amount of water; the solution was saturated with hydrogen chloride and then placed in the ice-box overnight. The colorless crystals were collected and dried over phosphorus pentoxide at 100° for 15 hours; m.p. 195–196.5° (lit., 190°). Neutral equivalent: Calc'd for $C_9H_6O_4$: 70. Found: 70.5.

7-Methoxy-1-acetonaphthone. Two grams of 7-hydroxy-1-acetonaphthone was treated with sodium hydroxide and dimethyl sulfate until no yellow coloration was obtained upon addition of sodium hydroxide. Sufficient ethanol was added to create a clear solution at room temperature, and the solution was placed in the ice-box overnight. The white prisms, m.p. 62–63°, after recrystallization from aqueous ethanol, had the sharp m.p. 63°; yield, 1.8 g.

Anal. Calc'd for $C_{11}H_{12}O_2$: C, 77.97; H, 6.00.

Found: C, 77.97; H, 6.11.

7-Methoxy-1-naphthoic acid (6). One gram of 7-methoxy-1-acetonaphthone was treated with a methanol-water solution of sodium hypochlorite (commercial Clorox), and the solution was worked up in the usual manner. One gram of an acid was obtained which melted at 165.5–168.5°. Recrystallization from aqueous ethanol gave long white needles, m.p. 168.5–169° (lit., 167–168°).

Anal. Calc'd for $C_{12}H_{10}O_3$: C, 71.27; H, 4.99.

Found: C, 71.12; H, 5.03.

7-Hydroxy-1-naphthoic acid (6, 7). 7-Methoxy-1-naphthoic acid (0.24 g.) was treated with 25 ml. of 12 *N* hydrochloric acid, and the mixture was heated under reflux for three hours. The solution was filtered hot and a small amount of white flocculent precipitate appeared in the cooled filtrate; m.p. 253–255°. Recrystallization from acetone-ligroin gave a white powder which softened at 253° and melted at 256°. Recrystallization from chlorobenzene gave fine colorless needles, m.p. 254–255° (lit., 253–254°).

7-Acetylamino-1-acetonaphthone (5). 7-Amino-1-acetonaphthone was acetylated by the method of Kaufman (29) to give needles, m.p. 149–150°.

7-Acetylamino-1-naphthoic acid (8). 7-Acetylamino-1-acetonaphthone (2.5 g.) dissolved in 25 ml. of dioxane was placed in a flask fitted with a stirrer and a dropping-funnel and surrounded by an ice-bath. One hundred grams of a solution containing 12.5 g. of iodine and 50 g. of potassium iodide per 100 g. of water was added with stirring over a period of one hour. Five grams of sodium hydroxide in 25 ml. of water was added in portions during this period. After the addition of the iodine solution, the reaction mixture was allowed to stand at room temperature overnight. A small amount of sodium bisulfite was added to destroy any excess sodium hypoiodite and the precipitated iodoform was removed. The orange-red filtrate was extracted with two 50-ml. portions of ether. The ether was evaporated on the steam-bath and the red oily residue was extracted with aqueous sodium bicarbonate. The sodium bicarbonate solution was decolorized with Darco and filtered. The filtrate was acidified carefully with hydrochloric acid; the precipitated acid had the m.p. 231–233°; yield, ca. 0.30 g. After two recrystallizations from aqueous ethanol, the white needles melted at 237–238° (lit., 229–230°).

Anal. Calc'd for $C_{12}H_{11}NO$: C, 68.13; H, 4.84; N, 6.11.

Found: C, 68.38; H, 4.93; N, 6.26.

7-Amino-1-naphthoic acid (8). About 0.20 g. of 7-acetylamino-1-naphthoic acid was treated with dilute hydrochloric acid and warmed on the steam-bath for one-half hour. The solution was filtered and neutralized with sodium hydroxide, after which it was reacidified with a very slight excess of acetic acid. This solution was then extracted with three portions of ether. The combined ether extracts, which showed a blue-green fluorescence, were evaporated to dryness and the residue extracted with benzene. An equal volume of ligroin was added to the benzene solution and after evaporation of a considerable portion of the benzene, crystallization occurred.

The light tan needles were washed with ligroin; m.p. 228.5–230° (lit., 223–224°).

SUMMARY

The structure of the product of Friedel-Crafts acetylation of acet-2-naphthalide has been proved to be 7-amino-1-acetonaphthone. The product of analogous acetylation of 2-bromo- or 2-chloro-naphthalene has been shown to be the corresponding 7-halo-1-acetonaphthone.

These conclusions have made necessary the revision of the structures of numerous related naphthalene derivatives described in the literature as 1,2-substituted compounds.

The function of halogen, acetylamino, and methoxyl groups in β -substituted naphthalenes, in directing the position of attack during Friedel-Crafts acylation, has been discussed.

URBANA, ILLINOIS

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CORRECTION OF STRUCTURE FOR SEVERAL SUPPOSED 2-SUBSTITUTED 1-NAPHTHALENE DERIVATIVES

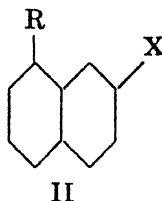
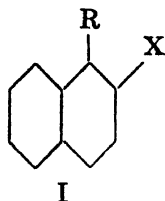
S. WINSTEIN, THOMAS L. JACOBS, AND BRUCE F. DAY

Received October 24, 1947

The work of Leonard and Hyson (1) indicates that the Friedel-Crafts acetylation of 2-acetamidonaphthalene (2) and 2-bromonaphthalene (2, 3) yields 8-acetyl derivatives, the 2-substituents [in contrast with the 1-substituents (4)] orienting the entering group to the unsubstituted ring. Thus it is necessary for us to correct the structures of several supposed 2-substituted 1-naphthalene derivatives.

In confirmation, we have found that the hypochlorite oxidation of the supposed 2-chloro-1-bromoacetanaphthone (2) yields an acid, m.p. 235-237° (uncorr.), undepressed on admixture with a sample of 7-chloro-1-naphthoic acid, m.p. 235-239° (uncorr.) available from the separation of the mixture of acids from the reaction of chlorobenzene with methyl furoate (5). Further, samples of the supposed α -di-*n*-butylaminomethyl-2-chloro-1-naphthalenemethanol hydrochloride, m.p. 124-124.5° [previously reported (2) 124.5-125°, 136.5-137°; two modifications], and the 7-chloro isomer, m.p. 123.5-125° [previously reported (6) 123-125°], melted at nearly identical temperatures. The mixed melting point showed no depression.

The necessary corrections involve change in structure from I to II



in the following cases (2): X = NHCOCH_3 , R = COCH_3 ; X = NH_2 , R = COCH_3 ; X = Cl, R = COCH_3 or COCH_2Br (7) or $\text{CH}(\text{OH})\text{CH}_2\text{Br}$ or $\text{CH}(\text{OH})\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ or $\text{CH}(\text{OH})\text{CH}_2\text{N}(\text{C}_4\text{H}_9)_2 \cdot \text{HCl}$ or $\text{CH}(\text{OH})\text{CH}_2\text{N}(\text{C}_6\text{H}_{11})_2 \cdot \text{HCl}$ or $\text{CH}(\text{OH})\text{CH}_2\text{N}(\text{C}_6\text{H}_{13})_2 \cdot \text{HCl}$; X = Br, R = COCH_2Br (7) or $\text{CH}(\text{OH})\text{CH}_2\text{Br}$ or $\text{CH}(\text{OH})\text{CH}_2\text{N}(\text{C}_4\text{H}_9)_2 \cdot \text{HCl}$.

LOS ANGELES 24, CALIFORNIA

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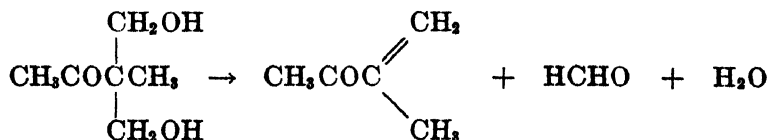
THE THERMAL DECOMPOSITION OF SOME
POLYMETHYLOL COMPOUNDS¹ROBERT W. BROWN² AND GREGG DOUGHERTY*Received June 2, 1947*

A number of investigators (1) have noted the relatively easy thermal decomposition, with and without catalysts, of compounds containing two or three methylol groups on the same carbon atom. In most cases these compounds were made by condensing formaldehyde with molecules containing hydrogen atoms made reactive by some adjacent activating group such as the carbonyl radical.

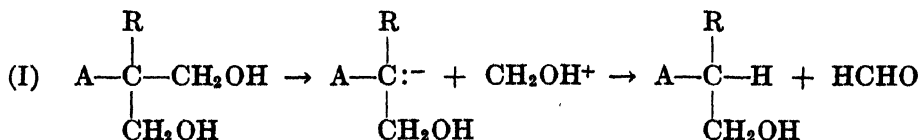
In compounds of the type
$$\begin{array}{c} \text{H} \\ | \\ \text{A}-\text{C}-\text{CH}_2\text{OH} \\ | \\ \text{CH}_2\text{OH} \end{array}$$
 where A is the activating group, dehydration by the usual methods applicable to aldols occurs readily. More interest-

ing for the present discussion are molecules such as
$$\begin{array}{c} \text{R} \\ | \\ \text{A}-\text{C}-\text{CH}_2\text{OH} \\ | \\ \text{CH}_2\text{OH} \end{array}$$
 where

dehydration does not occur, at least at the first stage of the decomposition. Here, in almost every instance reported, the compounds decompose rather easily with the loss of formaldehyde. For example, the dimethylol derivative of methyl ethyl ketone apparently follows this course, for when distilled with potassium acid sulfate it yields, according to Morgan and associates (1b), methyl isopropenyl ketone, formaldehyde, and water:



Since these reactions are usually carried out in the liquid state in the presence of a catalyst it is not unreasonable to suppose that they are ionic in nature, and proceed in the following manner:



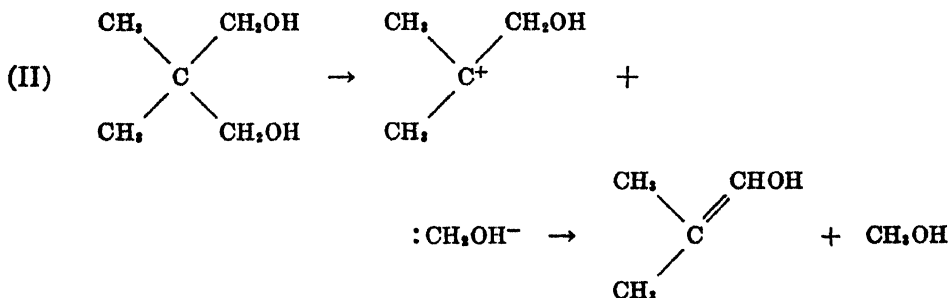
¹ From a thesis submitted to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree, Doctor of Philosophy.

² Present Address; Synthetic Rubber Division, United States Rubber Co., Naugatuck, Conn.

The positive methylol ion first formed loses a proton to the negative residue. The latter is then dehydrated to the final product. To facilitate later discussion this is called the type I reaction.

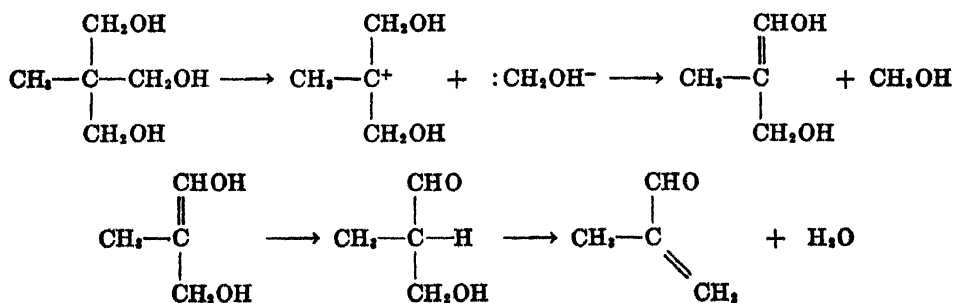
In the above example it seemed possible that the primary dissociation was conditioned by the electrophilic properties of the carbonyl or other activating group present, and it was therefore of interest to study the behavior of other polymethylol compounds in which such a group was absent. For this purpose the following were chosen: 2,2-dimethyl-1,3-propanediol, 2,2-dihydroxymethyl-1-propanol, and 2,2-dihydroxymethyl-1-butanol.

When 2,2-dimethyl-1,3-propanediol was heated with activated alumina at 200–210° the principal products were methanol and isobutyraldehyde. The latter was obtained in 70% yield. No isobutylene or isobutyl alcohol could be isolated, and only a trace of formaldehyde was detected. It is again a reasonable assumption that the first step in this process is the loss of a methylol group from the diol, but, if the reaction is ionic, it must in this case leave as the negative ion, since it acquires a proton from the residue and appears as methanol.



This may be called the type II reaction.

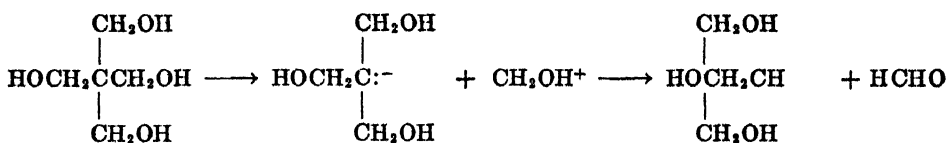
The 2,2-dihydroxymethyl-1-propanol decomposed completely to volatile products on heating at 240–270° with alumina. There was no tar formation, and the catalyst at the end of the reaction was dry and powdery. The principal products isolated were α -methylacrolein, methanol, and water. The yield of the acrolein derivative was 70% of theory. Formaldehyde was detected, but no isobutyraldehyde or α -methylallyl alcohol, to which the aldehyde has been shown to rearrange (2), could be found. Here also it appears that the proton goes to the methylol group or ion, and the residue then rearranges and loses water to give the final product:



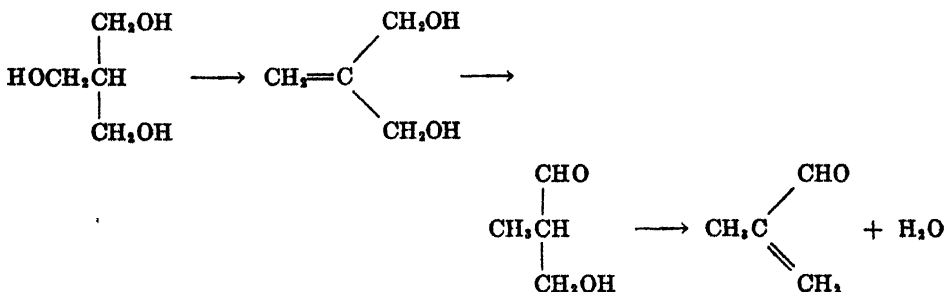
The 2,2-dihydroxymethyl-1-butanol, as might be expected, gave results entirely analogous to those obtained from the lower homolog; α -ethylacrolein was obtained in 60% yield, accompanied by methanol and water.

It is clear that the behavior of the two types of polymethylol compounds upon heating to the decomposition point in the presence of alumina differs sharply. The theoretical quantities of end products in the Type II reactions were never approached in any experiments, but the yields were surprisingly good considering the possibilities for complex condensations and polymerizations. The small amount of formaldehyde found indicated that the Type I decomposition could have occurred only to a very slight extent.

It was of interest to subject a compound midway between Type I and Type II to catalytic thermal decomposition. For this the easily available pentaerythritol and dipentaerythritol were chosen. Nef (3) reported, that in addition to much carbon monoxide and solid residue, a small amount of liquid boiling at 60–70° was obtained from the destructive distillation of pentaerythritol. He assumed that the liquid was acrolein. We have found that at 250–320° in the presence of activated alumina, pentaerythritol is decomposed into gaseous products containing much carbon dioxide, and a distillate consisting of α -methylacrolein, methanol, formaldehyde, and water. The amounts of α -methylacrolein were not high, ranging from 12 to 20%. However, when the reaction was conducted in the presence of copper-bronze rather than alumina, the yield of unsaturated aldehyde rose to 50% while that of methanol dropped sharply. The fact that the methanol decreases as the amount of α -methylacrolein increases strongly suggests that the latter is formed by a Type I mechanism:



The 2-hydroxymethyl-1,3-propanediol is then assumed to undergo dehydration to a molecule of a type which has been shown (2) to rearrange to an aldehyde under the conditions of the pyrolysis. A second dehydration then leads to the final product.



The formation of substantial amounts of methanol indicates that part of the pentaerythritol decomposed according to the Type II mechanism, in which the negative methylol group takes a proton from the residue. However, no other

fragment was found which might have resulted from the loss of methanol. The first product would be 2-hydroxymethyl-1-propanol-3-al. This is a β -hydroxy aldehyde with a hydrogen on the α carbon atom, and would be expected to undergo dehydration to 2-hydroxymethylpropenal-1. As no evidence for the presence of the latter compound, or of acrolein, to which it could revert by loss of formaldehyde, was found, it is postulated that due to the strong hydrogen bond acting between pentaerythritol molecules the escaping methylol group captures a proton from an adjacent molecule, causing condensation of the residues and accounting in part for the considerable amounts of polymeric material formed.

The decomposition of dipentaerythritol was not found to differ significantly from that of the monomer. Over alumina at 245–300° the same products were obtained, and the maximum yield of α -methylacrolein was 25%. Over copper powder the yield of aldehyde increased to 44%. Apparently the existence of one ether bond between two molecules of pentaerythritol does not materially change the course of decomposition.

EXPERIMENTAL PART^a

Materials. The pentaerythritol, dipentaerythritol, 2,2-dihydroxymethyl-1-propanol, and 2,2-dihydroxymethyl-1-butanol were supplied by the Heyden Corporation. The 2,2-dimethyl-1,3-propanediol was prepared by the action of an excess of formaldehyde on isobutyraldehyde in the presence of potassium hydroxide (4).

Pyrolysis. As the compounds studied all decompose at or below their boiling points pyrolysis in a static system was found to be satisfactory. Pentaerythritol, dipentaerythritol, and the trimethylol compounds were distilled from a Claisen flask heated in a metal-bath. The diol, which distills at atmospheric pressure without decomposition was decomposed in a flask surmounted by a short Vigreux column. A thermometer was inserted at the top of the column to give a rough check of the temperature of the distilling vapor. In the compounds investigated the maximum temperature of distillation was not above 110°.

The side arm of the flask or column led into a condenser which was connected to a receiver cooled in ice, followed by a trap immersed in acetone-Dry Ice. In experiments where decomposition into gaseous products was suspected a gas burette was connected to the Dry Ice trap.

In order to minimize polymerization of the unsaturated aldehydes the distillate was collected on about 0.2 g. of hydroquinone in each receiver, and the apparatus was flushed out with nitrogen before heating was begun.

Determination of α -methylacrolein. In reactions in which both α -methylacrolein and methanol were produced, it was found that the two distilled together as an azeotrope boiling at 59–61°. When the alcohol was removed by drying with calcium chloride, only small amounts of α -methylacrolein, b.p. 67–69° could be isolated, apparently because of polymerization and acetal formation. Partition between ether and water or between toluene and water was also not successful in separating the two. The amount of α -methylacrolein in the azeotrope was determined by distilling a middle cut of the azeotrope (b.p. 59.9–60.1°) onto a small amount of hydroquinone in a tared tube. The sample was weighed and transferred to a 250-ml. volumetric flask. Aliquots were analyzed for total carbonyl compounds with Brady's reagent according to the procedure of Iddles and Jackson (5). Analysis for formaldehyde with dimedone gave no weighable precipitate. A sample of the azeotrope was allowed to stand with saturated sodium bisulfite solution for two days, made alkaline to litmus, and distilled. The distillate gave a positive test for formaldehyde, and a

^a All melting points are corrected.

light precipitate with Brady's reagent, which was identified as the 2,4-dinitrophenylhydrazone of formaldehyde. Since no saturated aldehydes appear to be present, and the amount of formaldehyde is very small, it was assumed that the total carbonyl compound found was equal to the α -methylacrolein present. Two samples from different runs gave 75.5% and 77.0% aldehyde in the azeotrope.

2,2-Dimethyl-1,3-propanediol. Thirty-nine g. of the glycol was heated at 200–210° with 16 g. of activated alumina. Distillation took place slowly, the temperature of the distilling vapor remaining below 100°. The small amount of liquid which collected in the Dry Ice trap was allowed to come to room temperature with the trap connected to a wash bottle containing Brady's reagent, and another containing a very dilute solution of bromine in carbon tetrachloride. No decoloration of the bromine took place. Fractionation of the distillate after the addition of 10 ml. of water gave 28 g. of material boiling at 58–66°. Preliminary experiments had shown that two fractions came over in this range; an azeotrope of isobutyraldehyde and methanol, and methanol at 64–66°. In this run no attempt was made to separate the two. A weighed sample of the distillate was diluted and analyzed for isobutyraldehyde as described above. The 2,4-dinitrophenylhydrazone crystallized in yellow needles from ethyl acetate, m.p. 181–182°. A test for formaldehyde with resorcinol and sulfuric acid was negative. A sample of the distillate was dried with calcium chloride, the drying agent filtered off, dissolved in water, and distilled. The presence of methanol in the distillate was proved by oxidation to formaldehyde with a heated copper spiral and detection of the latter with resorcinol and sulfuric acid.

The aqueous solution remaining after removal of isobutyraldehyde and methanol was extracted with an equal volume of ether, the extract washed twice with saturated sodium bisulfite and dried over magnesium sulfate. Removal of the ether left only a small amount of oil, which did not distil at 160°. Distillation of the residual aqueous solution gave a distillate which contained formaldehyde, identified as the 2,4-dinitrophenylhydrazone, m.p. 164–165° after recrystallization from dilute alcohol (0.4 g. of derivative isolated).

2,2-Dihydroxymethyl-1-propanol. Twenty-five g. of 2,2-dihydroxymethyl-1-propanol and 10 g. of 100-mesh activated alumina were heated together at 240–250°. At the end of three hours the catalyst was completely dry. The distillate amounted to 25 g. Fractionation gave 13.7 g. of a fraction boiling at 59–63° and 2.0 g. boiling at 63–67°. No further distillate appeared until the temperature reached 94°, when a mixture of oil and water distilled.

The first fraction gave a precipitate upon reaction with 2,4-dinitrophenylhydrazine. Recrystallization from ethyl acetate gave short reddish needles, m.p. 200–201° (dec.). Semicarbazone, white needles from water, m.p. 196–197°. Shriner and Fuson (6) give 206° (dec.) and 198° respectively as the melting points of these derivatives of α -methylacrolein, but Nicholls and Pritchett (7) report 198–202° (dec.) and 194°. The decomposition point of the first depends markedly on the rate of heating.

The amount of aldehyde in the azeotrope was determined as described above. The presence of methanol was proved as in the decomposition of 2,2-dimethyl-1,3-propanediol.

The residue remaining after removal of α -methylacrolein and methanol was extracted with ether, dried over sodium sulfate, and the ether removed on a water-bath. The oily liquid remaining gave no distillate below 150° at atmospheric pressure. It was heated to 250° under 12 mm. pressure in an atmosphere of nitrogen. No distillate was obtained, and the oil had thickened to such an extent that bubbles no longer emerged from the capillary.

2,2-Dihydroxymethyl-1-butanol. Twenty-one g. of 2,2-dihydroxymethyl-1-butanol and 10 g. of alumina were heated at 250–260°. The distillate weighed 17 g. Two fractionations with an intervening drying gave 3.8 g. (76%) of methanol, b.p. 63–66°, and 7.9 g. (60%) of α -ethylacrolein, b.p. 75–82°, semicarbazone, white needles from dilute alcohol, m.p. 184–184.5°.

Pentaerythritol. In a typical run, 32 g. of pentaerythritol and 20 g. of 8–14-mesh activated alumina were heated at 270–280° until distillation ceased. The distillate was homogeneous, with a strong acrolein-like odor. It weighed 22.5 g., or 70% of the starting material. Fractionation gave 4.4 g. of material boiling at 57–63° and 2.1 g. of a fraction

boiling at 63–68°. The products were identified as α -methylacrolein and methanol as described above. Mixed m.p. of semicarbazone of product with that of crotonaldehyde, 176–179°.

Treatment of the residue as described above gave what was apparently the same intractable oil. The aqueous solution left after ether extraction was analyzed for formaldehyde with dimethyldihydroresorcinol. The amount found corresponds to 11 mole per cent of the pentaerythritol used.

Decomposition over copper powder. Forty g. of pentaerythritol and 8 g. of copper-bronze powder were heated together at 250–260° for two hours. At the end of this time, distillation had nearly ceased. The distillate consisted of two layers. They were separated and the aqueous layer extracted with 15 ml. of ether. The combined organic layers were dried over magnesium sulfate and fractionated. After removal of the ether, 2.5 g. of α -methylacrolein-methanol azeotrope and 9.0 g. of α -methylacrolein, b.p. 67–69° were obtained.

Dipentaerythritol. Thirty-two g. of dipentaerythritol was heated at 280–290° with 20 g. of 8–14-mesh alumina until distillation ceased. Twenty-two g. of homogeneous distillate was collected. Fractionation gave 5.7 g. of azeotrope, corresponding to 24% conversion to α -methylacrolein, and a methanol fraction of 1.1 g. As it appeared that fractionation might not be efficient in separating the azeotrope and methanol, the two fractions were combined, diluted to one liter and analyzed with Brady's reagent. The amount of aldehyde found in this manner corresponded to 25% of the theoretical.

Decomposition over copper powder. Thirty-two g. of dipentaerythritol and 5.5 g. of copper-bronze powder were heated at 250–260° until distillation ceased. The distillate formed two layers. They were separated and fractionated as described in the similar experiment with pentaerythritol. The fractionation gave 1.7 g. of azeotrope and 6.3 g. of α -methylacrolein.

SUMMARY

A study has been made of the decomposition of a series of polymethylol compounds in the presence of alumina and copper metal catalysts. Thermal decomposition of the methylol group has been shown to take place in two distinctly different ways, depending on the electronegativity of other groups in the molecule.

PRINCETON, N. J.

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A STUDY OF THE MECHANISM OF THE PIRIA REACTION¹

K. B. GOLDBLUM^{2a} AND R. E. MONTONNA^{2b}

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The action of sodium bisulfite on *alpha*-nitronaphthalene leads to the formation of sodium naphthionate together with smaller amounts of the sodium salt of 1-amino-2,4-naphthalene disulfonic acid and *alpha*-naphthylamine. This type of transformation was first investigated by Piria, (1) and later by Hunter and Sprung (2) and by Lauer, Sprung, and Langkammerer (3).

The mechanism which was suggested involves, in the case of *alpha*-nitronaphthalene, the types of addition shown in Chart I.

It is apparent that the formation of one mole of *alpha*-naphthylamine gives three moles of sodium bisulfate while in the production of naphthionic acid two moles of sodium bisulfate result and in the case of *alpha*-naphthylamine-2,4-disulfonic acid only one mole of sodium bisulfate is produced.

The present study shows that the amount of sodium bisulfate actually corresponds to that predicted on the basis of this mechanism.

EXPERIMENTAL WORK

The Overall Standard Procedure of Hunter and Sprung (1) was used. A typical experiment follows:

A seven-gram sample (0.04 mole) of *alpha*-nitronaphthalene (m.p. 59–61°) was treated with twice the theoretical amount of sodium bisulfite (0.24 mole) in a total of 100 ml. of aqueous solution in a one-liter, round-bottom, three-necked flask equipped with a mercury-sealed mechanical stirrer and a reflux condenser. An absorption train containing dilute sodium hydroxide to absorb any sulfur dioxide evolved was connected to the top of the reflux condenser. The solution was refluxed for about five hours (until no odor of *alpha*-nitronaphthalene could be detected and the solution was homogeneous.)

The reaction mixture was then cooled and its volume was quickly determined. Portions of this solution were pipetted for the various sulfur determinations.

The volume of the remainder of the solution (about two-thirds) was measured and this was treated with 10 ml. of concentrated hydrochloric acid and boiled to expel the sulfur dioxide. The mixture was cooled, and the precipitated naphthionic acid was removed by filtration. This crude material was added to 100 ml. of water, brought to a boil, cooled, and again filtered. This precipitate (naphthionic acid) was dried at 120°, weighed, and ground in a mortar for analysis.

The filtrate and the washings from the naphthionic acid were combined and evaporated to dryness. This product was weighed and ground in a mortar for analysis. It contained 2,4-disulfonic acid, *alpha*-naphthylamine hydrochloride, a trace of naphthionic acid, sodium chloride, and sodium sulfate. This material will be called the "disulfonic acid fraction".

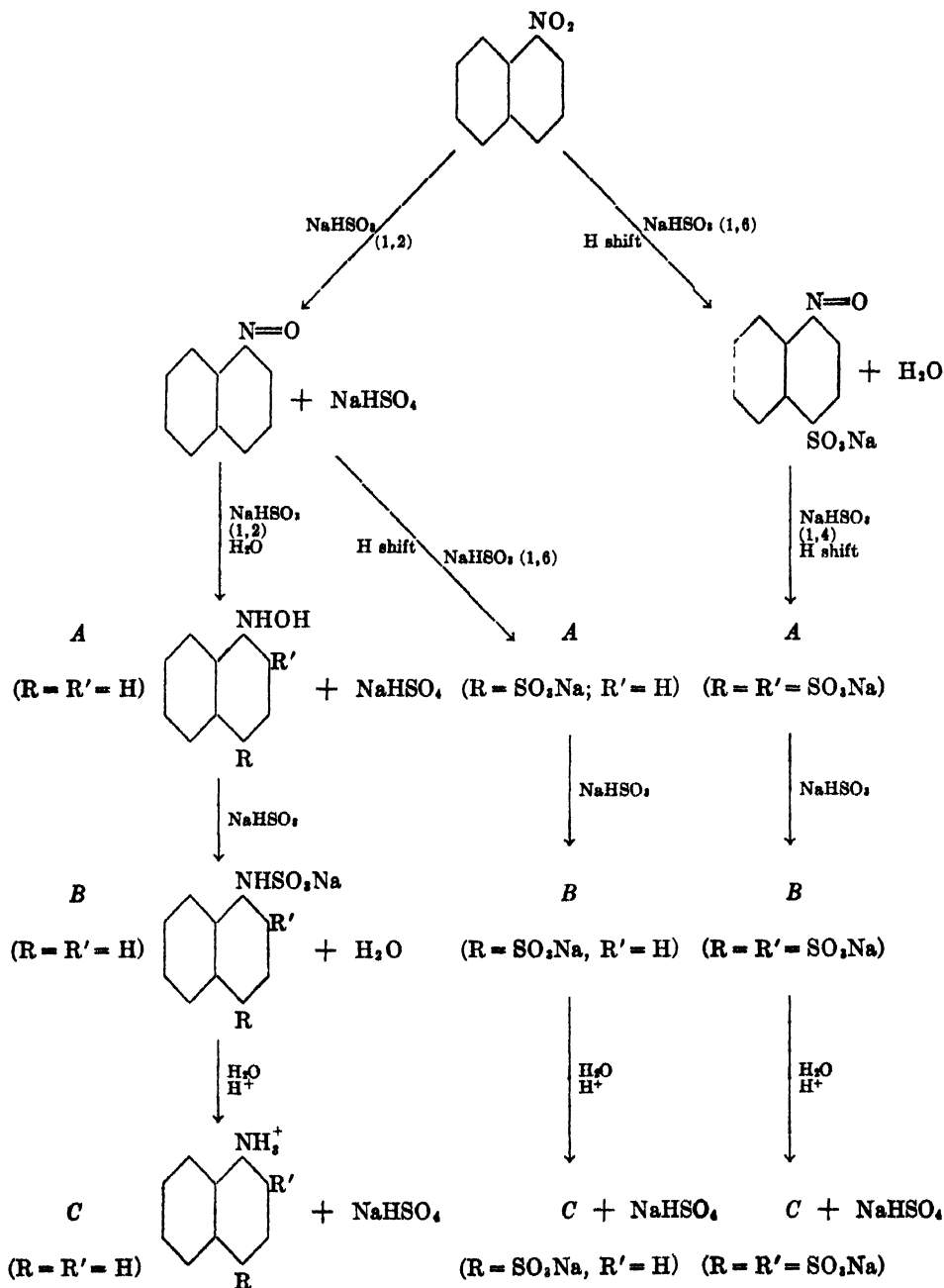
The amounts of nitrogen in the naphthionic acid and in the disulfonic acid fraction were

¹ Abstracted from a thesis submitted by Kenneth B. Goldblum to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

² Present addresses: a. General Electric Company, Pittsfield, Massachusetts. b. Institute of Industrial Research, Syracuse University, Syracuse, New York.

determined by the Kjeldahl-Arnold-Gunning method and expressed either as per cent purity of the substance under examination or as ml. of 0.1253 *N* alkali ($N \times 5.7$).

CHART I



Sulfur balance. The sources of sulfate which are important in the present work are: (a) Sulfate in the original sodium bisulfite stock solution. (b) Sulfate formed in the reac-

tion. (c) Sulfate from naphthionic acid. (d) Sulfate from the disulfonic acid fraction. They were determined as follows:

a. Sulfate in the original stock solution was determined by treating pipetted portions with concentrated hydrochloric acid, then boiling to remove all of the sulfur dioxide. Precipitation with barium chloride gave the original sulfate in terms of grams of barium sulfate per ml. of stock solution.

b. Sulfate formed in the reaction was determined by treating a pipetted portion of the reaction mixture with hydrochloric acid and boiling to remove all of sulfur dioxide. Precipitation with barium chloride as above gave the original sulfate plus the sulfate formed in the reaction. When the sulfate in the original sodium bisulfite stock solution is subtracted from the above total the difference (between b and a) is the sulfate formed in the reaction.

c. Sulfate equivalent to the naphthionic acid was calculated from the nitrogen as determined by the Kjeldahl-Arnold-Gunning method.

d. The sulfur in the disulfonic acid fraction was determined by precipitating the inorganic sulfate in a weighed portion. Another weighed sample was subjected to the action of Eschka mixture and heated. Treatment with bromine water and hydrochloric acid, followed by boiling to expel all excess bromine and carbon dioxide, was then followed by precipitation with barium chloride. The Eschka treatment gives the total sulfur, both organic and inorganic. Subtraction of the value for the inorganic sulfur leaves the organic sulfur.

When the nitrogen to organic sulfur ratios of the disulfonic acid fraction were determined, they were found to be over 0.5. This high ratio demonstrates that (excluding a very small amount of naphthionic acid present) there was some *alpha*-naphthylamine present. Consequently, the *alpha*-naphthylamine was removed by steam distillation from an alkaline solution of a weighed portion of the disulfonic acid fraction. After this treatment, nitrogen to organic sulfur ratios were very close to 0.5 which they should be if they represent only disulfonic acid.

CALCULATIONS

A method was devised for calculating the amount of *alpha*-naphthylamine and disulfonic acid in the disulfonic acid fraction without determining either of them. The method is based on the following known data:

1. The amount of pure naphthionic acid produced.
2. The total nitrogen in the disulfonic acid fraction.
3. The total sulfate formed in the reaction.

Let a = grams of naphthionic acid produced.

b = total grams of sulfate as barium sulfate.

c = total nitrogen in the disulfonic acid fraction expressed as ml. of 0.1253 N alkali ($N \times 5.7$).

x = grams of *alpha*-naphthylamine in the disulfonic acid fraction.

y = grams of disulfonic acid in the disulfonic acid fraction.

Molecular weights used in the calculations are as follows:

Barium sulfate = 233; Naphthionic Acid = 223, Disulfonic acid monosodium salt = 325; *alpha*-Naphthylamine = 143.

The *nitrogen balance* will then be:

Nitrogen from *alpha*-naphthylamine plus nitrogen from disulfonic acid equals total nitrogen in the disulfonic acid fraction, or in symbols:

$$\frac{14x}{143} + \frac{14y}{325} = \frac{14 \times 0.1253c}{1000} \quad (\text{I})$$

from which

$$2.2908 x + y = 0.04105 c \quad (\text{II})$$

The *sulfur balance* will then be:

Sulfate from the formation of disulfonic acid plus the sulfate from the formation of *alpha*-naphthylamine = total sulfate formed minus the sulfate derived from naphthionic acid formation, or (in symbols):

$$\frac{233y}{325} + \frac{3 \times 233x}{143} = b - \frac{2 \times 233a}{223} \quad (\text{III})$$

which gives

$$6.8662x + y = 1.40481b - 2.93533a \quad (\text{IV})$$

Solving (II) and (IV) simultaneously gives

$$x = 0.307085b - 0.641543a - 0.00897202c \quad (\text{V})$$

Once x is calculated from known data, then from equation (II),

$$y = 0.04105c - 2.2908x \quad (\text{VI})$$

One of the assumptions on which these equations depend is that the only substances in the disulfonic acid fraction containing nitrogen are *alpha*-naphthylamine and disulfonic acid. However, some naphthionic acid might be present due to imperfect washing and in that case, its presence would be detected by a nitrogen to organic sulfur ratio over 0.5. The amount of naphthionic acid in the disulfonic acid can be calculated from the N to S ratio as follows:

Let n = weight fraction of naphthionic acid

$1-n$ = weight fraction of disulfonic acid

then

$$\frac{\frac{n}{223} + \frac{1-n}{325}}{\frac{n}{223} + \frac{2(1-n)}{325}} = r = (N/S \text{ ratio}) \quad (\text{VII})$$

Simplifying gives:

$$\frac{102n + 223}{446 - 121n} = r \quad (\text{VIII})$$

As an example, in experiment 82,

$r = 0.50207$, $n = 0.0056726$ and the weight of "disulfonic acid fraction" is 23.997, then $23.997 \times 0.0056726 = 0.1361$ grams of naphthionic acid in the disulfonic acid fraction. The sulfate in the disulfonic acid fraction = 12.4067 grams of barium sulfate. The sulfate due to disulfonic acid is

$$12.4067 - 0.1361 \times \frac{233}{223} = 12.2645 \text{ grams}$$

The ml. of 0.1253 N alkali which are equivalent to this amount of barium sulfate are

$$\frac{0.5 \times 12.2645 \times 1000}{233 \times 0.1253} = 210.04 \text{ ml.}$$

The ml. of 0.1253 N alkali equivalent to the naphthionic acid fraction are

$$\frac{0.1361 \times 1000}{223 \times 0.1253} = 4.87 \text{ ml.}$$

The total nitrogen from naphthionic acid and disulfonic acid in the disulfonic acid fraction is equivalent to $210.04 + 4.87 = 214.91$ ml. However, the nitrogen by analysis from the disulfonic acid fraction is 259.89 ml. The nitrogen due to *alpha*-naphthylamine is equivalent to $259.89 - 214.91 = 44.9$ ml.

TABLE I

	81	82	83	86
N/S ratio.....	0.47200	0.50207	0.56409	0.50381
n.....	0.0000	0.0058726	0.16789	0.010426
Naphthionic acid in disulfonic acid fraction, g.....	0.00	0.1360	4.266	0.3378
BaSO ₄ due to naphthionic acid.....	0.00	0.1422	4.457	0.3530
0.1253 $\frac{1}{2}$ N alkali equiv. to naphthionic acid, ml.....	0.00	4.871	152.657	12.091
Total BaSO ₄ in disulfonic acid fraction.....	11.9267	12.4067	9.9286	11.5677
Total N in disulfonic acid fraction...	251.550	259.891	243.387	242.696
N in α -naphthylamine.....	47.312	44.975	0.000	38.539
Sulfate from disulfonic acid.....	5.963	6.132	2.736	5.607
Sulfate from α -naphthylamine...	4.145	3.939	0.000	3.375
Sulfate from naphthionic acid.....	3.604	2.977	11.901	3.034
Total calculated sulfate.....	13.712	13.048	14.637	12.722
Total analytically determined sulfate.....	13.070	13.601	13.737	13.802
a.....	1.724	1.425	5.696	1.790
b.....	13.070	13.601	13.737	13.802
c.....	251.550	255.020	90.730	230.605
x.....	0.6501	0.9818	0.2504	1.020
y.....	8.8368	8.2194	4.2981	7.129
BaSO ₄ in naphthionic acid. Disulfonic acid fraction.....	0.000	0.142	4.457	0.3530
BaSO ₄ in disulfonic acid.....	12.671	11.785	6.163	10.222
Total BaSO ₄ in disulfonic acid fraction calculated.....	12.671	11.927	10.620	10.575
Total BaSO ₄ analytically determined	11.927	12.4067	9.929	11.568
Disulfonic acid fraction weight	24.375	23.997	25.406	32.403

TABLE II
SCHEDULED SUMMARY OF EXPERIMENTAL DATA

SERIAL NO.	SULFATE FORMED		SULFATE IN DISULFONIC ACID FRACTION	
	Calc'd	Exper. Deter.	Calc'd	Exper. Deter.
81	13.712	13.070	12.671	11.927
82	13.048	13.601	11.927	12.407
85	14.637	13.737	10.620	9.929
86	12.722	13.802	10.575	11.568
Average.....	13.505	13.553	11.448	11.458

The weight of α -naphthylamine is:

$$\frac{44.985 \times 0.1253 \times 143}{1000} = 0.8059 \text{ grams}$$

The following tabulation can now be made.

Sulfate as barium sulfate from disulfonic acid formation:

$$\frac{210.04 \times 0.1253 \times 233}{1000} = 6.132 \text{ grams}$$

Sulfate from naphthylamine formation:

$$\frac{44.98 \times 0.1253 \times 3 \times 233}{1000} = 3.939 \text{ grams}$$

Sulfate from naphthionic acid formation:

$$(1.390 \times 0.927 + 0.1361) \times \frac{2 \times 233}{223} = 2.977 \text{ grams}$$

(The naphthionic acid was 92.7% pure by analysis.)

The total $6.132 + 3.939 + 2.977 = 13.048$ grams. Actually 13.601 grams of sulfate as barium sulfate was obtained by analysis.

Reversing the procedure and starting with the sulfate formed in the reaction, the naphthionic acid in the naphthionic acid fraction plus that in the disulfonic acid fraction, and the total nitrogen in the disulfonic acid fraction, we can calculate the amount of disulfonic acid. From this a check can be made on the amount of sulfate in the disulfonic acid fraction.

If we use the following values for a, b, and c

$a = (1.390 \times 0.927) + 0.1361 = 1.4251$, $b = 13.601$, and $c = 259.891 - 4.87 = 255.02$.

Then, $x = 0.9818$ grams of *alpha*-naphthylamine,

$y = 8.2194$ grams of disulfonic acid.

The sulfate in the disulfonic acid fraction is calculated from the naphthionic acid part and from the disulfonic acid.

Sulfate as barium sulfate in naphthionic acid:

$$0.136 \times \frac{233}{223} = 0.142 \text{ grams}$$

Sulfate in disulfonic acid: $8.2194 \times 2 \times \frac{233}{223} = 11.785$ grams

The total is $0.142 + 11.785 = 11.927$ grams as compared to the analytical value of 12.4067 grams.

A summary of four experiments may be seen in Table I. Since all of these experiments began with the same amount of *alpha*-nitronaphthalene, it is reasonable to average these values (see Table II).

CONCLUSIONS

The above figures which show excellent agreement between the calculated values and the experimentally determined values of the sulfate formed in the reaction and the sulfate in the disulfonic acid fraction are in agreement with the views of Langkammerer and Lauer, and Hunter and Sprung.

The amount of sulfate formed in the reaction bears the relation to the various products that is predicted by this mechanism, and the calculations presented here show that when the proposed mechanism is assumed and the amount of sulfate formed in the reaction is taken as the basis of calculation, the amount of sulfur

appearing as organic sulfur in the disulfonic acid fraction is in agreement with the analytical values.

MINNEAPOLIS 14, MINN.

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THE SOLUBILITIES OF LONG-CHAIN DIALKYLDIMETHYL-AMMONIUM CHLORIDES IN ORGANIC SOLVENTS

A. W. RALSTON, R. A. RECK, H. J. HARWOOD, AND P. L. DUBROW

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The fact that the quaternary ammonium halides are true salts has a decided influence on their solubilities in organic solvents. It has recently been shown (1) that dodecyl- and octadecyl-trimethylammonium chlorides possess limited solubilities in the non-polar and slightly polar organic solvents with the exception of carbon tetrachloride and chloroform, and that they are appreciably soluble in polar organic solvents. These solubility behaviors are explainable on the basis of their salt-like properties. The replacement of a methyl group in the alkyltrimethylammonium chlorides by a second long-chain radical should yield a series of compounds which possess interesting solubility characteristics. Although the higher dialkyldimethylammonium chlorides are salts, the presence of the two long chains should materially increase their solubilities in the non-polar and slightly polar organic solvents. In the present study we have determined the solubilities of dioctyl-, didecyl-, didodecyl-, ditetradecyl-, dihexadecyl-, and octyldodecyl-dimethylammonium chlorides in a variety of organic solvents of varying polarities. These observations have enabled us to formulate some generalizations regarding the solubilities of the higher alkyl quaternary ammonium chlorides.

EXPERIMENTAL

Preparation of dioctyl-, didecyl-, didodecyl-, ditetradecyl-, and dihexadecyl-dimethylammonium chlorides. All these quaternary ammonium salts were similarly prepared. The preparation of didodecyldimethylammonium chloride will be described in detail as an example of the procedure employed.

Predistilled dodecylamine was carefully fractionated through a Stedman-packed column. In a two-necked flask fitted with a mercury-sealed stirrer and an air condenser, 212 g. of this distilled amine (f.p. 28.26°) and 8.5 g. of 50% Raney nickel suspended in dodecylamine were heated with stirring at 200° for 2.5 hours. The resulting product was taken up in ethyl acetate, the Raney nickel removed by filtration, and the didodecylamine crystallized from the solvent.

To 77 g. of the recrystallized didodecylamine dissolved in 200 cc. of ethanol, 49 cc. of 85% formic acid was slowly added, the temperature being maintained at about 40°. After this addition, 46 cc. of a 36% aqueous formaldehyde solution was added and the temperature raised to 60°. After the evolution of carbon dioxide had subsided, the temperature was maintained at the reflux point of the solution for one-half hour. The solution was then neutralized with aqueous sodium hydroxide, and the top layer was drawn off, dried over anhydrous potassium carbonate, filtered, and distilled (b.p. 183° at 0.35 mm.). The didodecylmethylamine so obtained (f.p. 10.4°) was dissolved in ethyl acetate, methyl chloride was added, and the mixture was heated in a bomb at 80° for one hour. The didodecyldimethylammonium chloride was recrystallized twice from ethyl acetate to give a white, crystalline, hygroscopic product. Dioctyldimethyl- and didecyldimethyl-ammonium chlorides are extremely hygroscopic. This property was not observed with ditetradecyldimethyl- and dihexadecyldimethyl-ammonium chlorides.

Preparation of octyldodecyldimethylammonium chloride. To 102 g. of dodecyl chloride dissolved in 50 cc. of ethanol was added 38.7 g. of methylamine and the solution was heated in a bomb at 125° for eight hours. The contents of the bomb were neutralized with aqueous sodium hydroxide, the top layer dissolved in Skellysolve F, dried over anhydrous potassium carbonate, filtered, and the methyl dodecylamine distilled. To 64 g. of distillate was added 56.3 g. of freshly distilled octyl bromide and the mixture was heated at 90° for five hours. One-half of the theoretical amount of aqueous sodium hydroxide required for complete neutralization was added at the end of 2.5 hours and the remainder added slowly during the last 2.5 hours. The top layer was extracted with Skellysolve F, dried over anhydrous potassium carbonate, filtered, and the octyldodecylmethylamine distilled (b.p. 170° at 0.25 mm.). This distillate was converted to the quaternary ammonium chloride by heating with methyl chloride in a bomb at 80° for one hour. The product was recrystallized twice from cold ethyl acetate. Octyldodecyldimethylammonium chloride is very hygroscopic.

The solubilities were determined in sealed tubes by the method and with the apparatus previously described (2, 3, 4).

RESULTS AND DISCUSSION

The solubility behavior of the higher dialkyldimethylammonium chlorides in the non-polar solvent hexane is extremely interesting. Dioctyl-, didecyl-, and octyldodecyl-dimethylammonium chlorides are essentially insoluble in this solvent and thus exhibit the solubility characteristics of salts. On the other hand, their higher homologs, didodecyl-, ditetradecyl-, and dihexadecyl-dimethylammonium chlorides function as typical organic non-electrolytes, their solubilities decreasing with increase in chain lengths. The solubilities in hexane increase rapidly over a small temperature range; for example, that of didodecyl-increases from 4.16 to 186 g. per 100 g. of solvent over the temperature interval 31° to 34°, ditetradecyl- from 3.1 to 150 g. between 42° and 44°, and dihexadecyl-dimethylammonium chloride from 5.2 to 108 g. between 52° and 54°.

The solubilities of the dialkyldimethylammonium chlorides in benzene do not exhibit the discontinuities encountered in hexane. The lower members, dioctyl-, didecyl-, and octyldodecyl-dimethylammonium chlorides are extremely soluble in benzene and could not be induced to crystallize below the freezing point of the solvent. The higher homologs are also appreciably soluble in benzene, the solubilities decreasing with increase in chain lengths. Some of the observed values are as follows: didodecyl-, 1.1 g. in 100 g. solvent at 5°, 39.5 g. at 10°; ditetradecyl-, 4.7 g. at 20°, 78.5 g. at 30°; dihexadecyl-, 1.0 g. at 30°, 85.5 g. at 40°. The solubilities of these compounds in benzene are, therefore, quite similar to those of the higher alkyl non-electrolytes and are in contrast to those of the higher alkyltrimethylammonium chlorides, which are only slightly soluble in this solvent.

The higher alkyltrimethylammonium chlorides have been shown (1) to be extremely soluble in the chlorinated solvents chloroform and carbon tetrachloride. The higher dialkyldimethylammonium chlorides are likewise very soluble in chloroform, and only didodecyl-, ditetradecyl-, and dihexadecyl-dimethylammonium chlorides give well-defined solubility curves, Fig. 1. Although the dialkyldimethylammonium chlorides are not so soluble in carbon

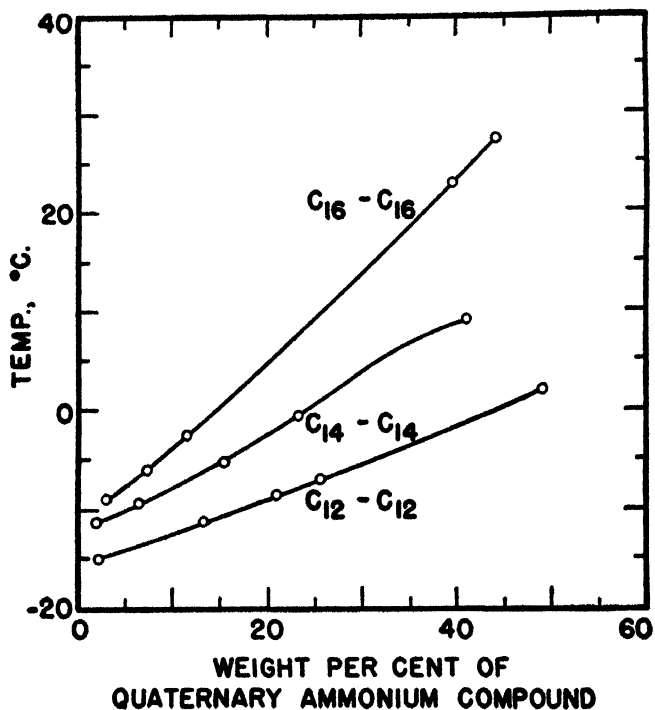


FIG. 1. SOLUBILITIES OF DIALKYLDIMETHYLAMMONIUM CHLORIDES IN CHLOROFORM

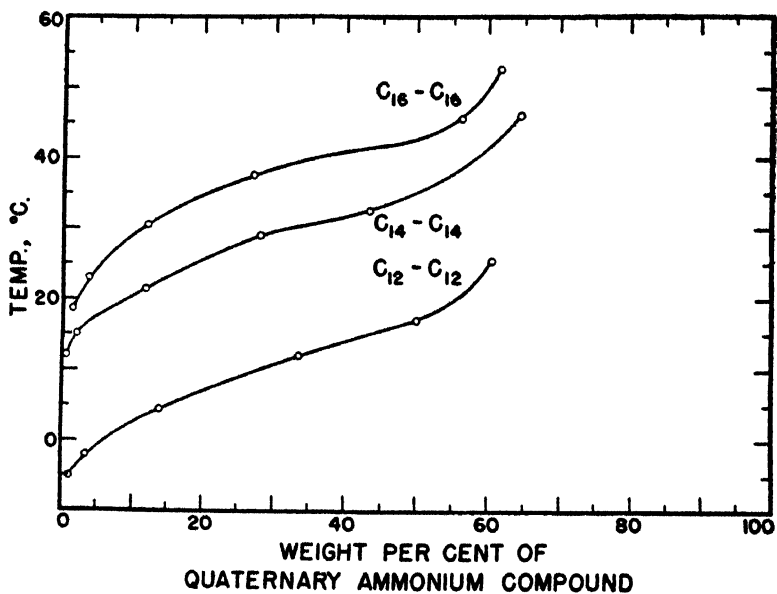


FIG. 2 SOLUBILITIES OF DIALKYLDIMETHYLAMMONIUM CHLORIDES IN CARBON TETRACHLORIDE

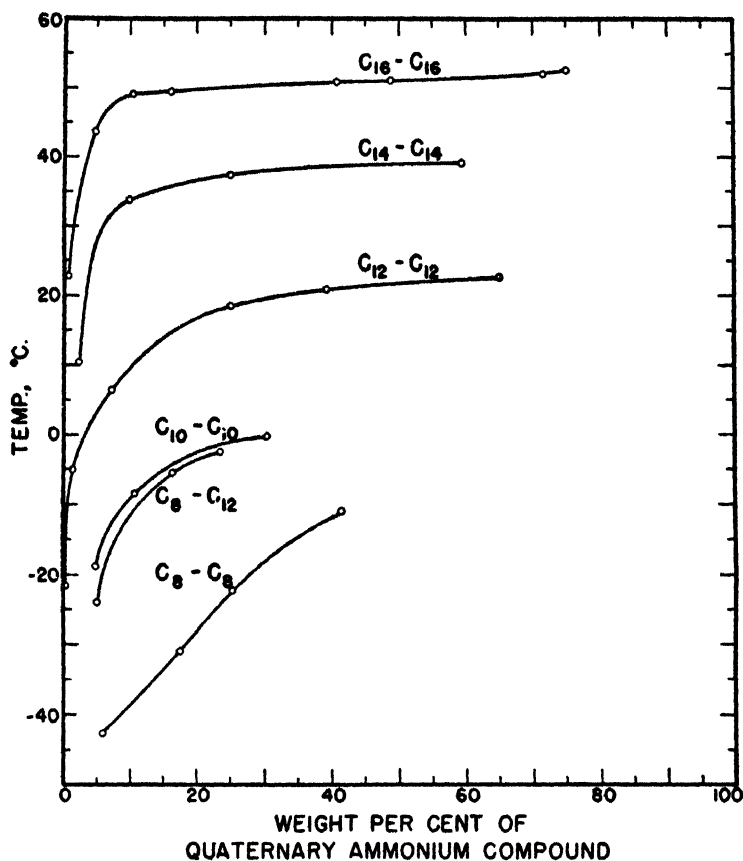


FIG. 3. SOLUBILITIES OF DIALKYLDIMETHYLAMMONIUM CHLORIDES IN ACETONITRILE

TABLE I
SOLUBILITIES OF DIALKYLDIMETHYLAMMONIUM CHLORIDES IN METHANOL
AND ACETONE

SALT	SOLVENT	SOLUBILITY IN 100 G. OF SOLVENT
Didodecyl-	Methanol	0.5- ^{80°} , 0.7- ^{70°} , 1.1- ^{60°} , 4.1- ^{50°} , 13.6- ^{40°} , 49.6- ^{30°} , 119.7- ^{20°} 312.9- ^{10°}
Ditetradecyl-	Methanol	1.1- ^{40°} , 5.7- ^{30°} , 12.9- ^{20°} , 29.0- ^{10°} , 146.9 ^{0°} , 257.1 ^{10°}
Dihexadecyl-	Methanol	3.6- ^{10°} , 10.4 ^{0°} , 30.7 ^{10°} , 163.2 ^{20°}
Octyldodecyl-	Acetone	4.8- ^{10°} , 17.8- ^{30°}
Didecyl-	Acetone	4.7- ^{10°} , 17.6- ^{30°}
Didodecyl-	Acetone	2.6 ^{10°} , 55.0 ^{20°}
Ditetradecyl-	Acetone	3.6 ^{20°} , 78.5 ^{40°}
Dihexadecyl-	Acetone	3.1 ^{40°} , 92.3 ^{50°}

tetrachloride, Fig. 2, as in chloroform the lower members could not be crystallized from this solvent.

All the higher alkyl quaternary ammonium chlorides investigated are extremely soluble in polar organic solvents. They are appreciably more soluble in methanol than in acetone, and the lower members could not be crystallized from the former solvent. Their solubilities in methanol and acetone are shown in Table I.

The higher dialkyldimethylammonium chlorides are appreciably less soluble in acetonitrile than in methanol, their solubilities decreasing greatly with increase in chain lengths. Their comparative solubilities in these two solvents are similar to those previously observed (1) for the alkyltrimethylammonium chlorides. The solubilities of the higher dialkyldimethylammonium chlorides in acetonitrile are shown in Fig. 3. It will be noted that the solubility of octyldodecyldimethylammonium chloride is quite similar to that of didecyldimethylammonium chloride and much greater than that of didodecyldimethylammonium chloride. This indicates that the solubility of these compounds is influenced more by the total number of carbon atoms in the two chains than by the length of the longest chain.

Few series of organic compounds show the wide range of solubilities which has been observed with the higher dialkyldimethylammonium chlorides. The fact that they are appreciably soluble in both polar and non-polar solvents is predictable from their structures.

SUMMARY

The solubilities of dioctyl-, didecyl-, didodecyl-, ditetradecyl-, dihexadecyl-, and octyldodecyl-dimethylammonium chlorides have been determined in hexane, benzene, chloroform, carbon tetrachloride, methanol, acetone, and acetonitrile.

Certain comparisons have been made between the solubilities of these compounds and those of the alkyltrimethylammonium chlorides.

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THE OPTICAL RESOLUTION OF AMIDONE¹WALLACE R. BRODE AND MAX W. HILL²*Received September 4, 1947*

Amidone, 6-dimethylamino-4,4-diphenyl-3-heptanone, possesses one asymmetric carbon atom and thus is capable of existing in a dextro, levo, and racemic form. The isolation of these optical forms is desirable, since they may possess different physiological activity.

The only crystalline salt obtained of Amidone and an optically active acid was the acid *d*-tartrate. The diastereo compound of this salt appears to be the more stable. It is deposited from various solvents under a variety of conditions in small rosettes, m.p. 135.0–138.5°, $[\alpha]_D^{25} +10.00^\circ$. However, one sample of this salt dissolved in a mixture of ethyl acetate and ether deposited, after a period of three months at room temperature, some long, fine needles as well as the rosettes. Careful isolation and recrystallization of the needles gave a salt, m.p. 149.5–151.0°, $[\alpha]_D^{26} -84.43^\circ$.

It was found that either the rosettes or needles could be obtained from a saturated acetone solution of the salt, depending on the type of crystal used to seed the solution. Such a separation appears to depend more on the rate of crystallization induced by one form, than on the difference in solubility of the two forms. This phenomenon has been observed previously for other resolutions using tartaric acid by Brode and Wernert (1).

Seeding of a saturated acetone solution of the salt with the needles gave *l*-Amidone-*d*-acid tartrate. The mother liquor was then seeded with the rosettes and the diastereo compound was deposited, leaving the resulting mother liquor rich in *d*-Amidone-*d*-acid tartrate. Recovery of the free base from the *l*-Amidone-*d*-acid tartrate gave *l*-Amidone, m.p. 98.7–99.0°, $[\alpha]_D^{22} -29.91^\circ$. Recovery of the free base from the enriched *d*-Amidone-*d*-acid tartrate gave enriched *d*-Amidone, m.p. 75.5–96.4°, $[\alpha]_D^{25} +17.55^\circ$. The melting point obtained for racemic Amidone was 76.9–77.8°. Thus, the racemic compound and the phase diagram of composition plotted against melting point should possess two eutectic points (2). Therefore it should be possible to melt the eutectic mixture away from the pure dextro isomer. This was accomplished by an electrically heated Büchner funnel and the pure *d*-Amidone was obtained, m.p. 98.7–99.0°, $[\alpha]_D^{26} +29.51^\circ$.

The comparison of the rotatory dispersion of the dextro and levo Amidone and the corresponding hydrochloride salts is given in Figure 1. The observed rotations for the *d*- and *l*-Amidone hydrochlorides for the D line were $[\alpha]_D^{28} +127.5^\circ$ and -127.8° ($c = 2.96$ in water)³.

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² Wm. S. Merrell Fellow under the Ohio State University Research Foundation.

³ Subsequent to submission of this paper for publication, a note has appeared in *Nature*, 160, 605 (1947), (Nov. 1, 1947), by Thorp, Walton and Ofner describing a different method of resolution of Amidone. They obtained for the *d*- and *l*-Amidones $[\alpha]_D^{26} +28^\circ$ and -32° ; and for the hydrochlorides $[\alpha]_D^{26} +143^\circ$ and -145° .

EXPERIMENTAL

Amidone acid tartrate (30.0 g. 0.065 mole) in 400 ml. of acetone was prepared by dissolving 20.0 g. (0.065 mole) of racemic Amidone in 100 ml. of acetone and mixing at room temperature with 10.0 g. (0.067 mole) of *d*-tartaric acid in 300 ml. of acetone. The solution was cooled to 8° in an ice-box and seeded with the needles, m.p. 149.5–151.0°. After 36 hours, 10.3 g. of salt had crystallized, m.p. 142.8–145.0°. Fractionation of this salt from acetone gave 8.7 g. of nice white needles, m.p. 149.5–151.0°, $[\alpha]_D^{25} -84.43^\circ$ ($c = 3.02$ g., $l = 2$ dcm., in distilled water).

The mother liquor, without change in concentration, was seeded with the rosettes, m.p. 135.0–138.5° (*dl*-Amidone-*d*-acid tartrate) and placed in the ice-box at 8° for 48 hours. Rosettes were deposited, 8.7 g., m.p. 130–135°, $[\alpha]_D^{25} +26.32^\circ$ ($c = 3.02$ g., $l = 2$ dcm., in distilled water). The mother liquor from this fraction had a specific rotation of *ca.* 56° (estimated concentration in acetone).

Concentration of this mother liquor and several days standing in the ice-box failed to produce further crystallization. The acetone was removed under vacuum and the free

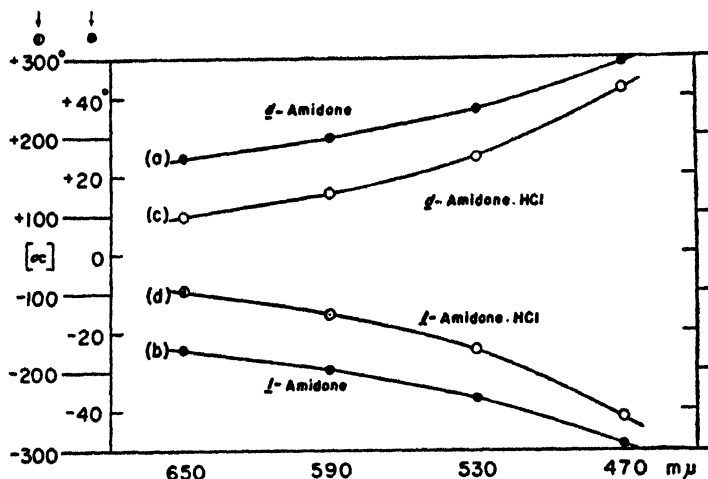


FIG. 1. ROTATORY DISPERSION OF *d*- AND *l*-AMIDONE (●) (a AND b) AND *d*- AND *l*-AMIDONE HYDROCHLORIDE (○) (c AND d)

dextro-rich Amidone base recovered, 7.0 g. (11.0 g. of Amidone acid tartrate would yield 7.2 g.), m.p. 75.5–96.4°, $[\alpha]_D^{25} +17.55^\circ$ ($c = 3.02$ g., $l = 2$ dcm., absolute ethanol).

The pure levo-Amidone was recovered from the *l*-Amidone-*d*-acid tartrate salt (5.85 g. from 8.7 g., 100% yield), m.p. 98.7–99.0°, $[\alpha]_D^{25} -29.91^\circ$ ($c = 2.66$ g., $l = 2$ dcm., absolute ethanol).

The dextro-rich Amidone is composed of 79.3% of the dextro isomer and 20.7% of the levo isomer.

An electrical heating mantle was built around a seven-centimeter Büchner funnel. The heating element was controlled by a 110-volt, 5-ampere Variac and calibrated for voltage-temperature readings. Five 7.0-cm., No. 1 Whatman filter papers were first placed in the funnel, followed by a 3.0 g. layer of the dextro-rich Amidone and five more filter papers. The funnel was placed on a suction flask, a rubber dam placed on top and the vacuum of a water aspirator applied. The temperature was raised rapidly to 75.5° and then slowly to 94°. The filter press was taken apart and yielded 1.09 g. of solid cake from between the center filter papers. Melting point data indicated the edge of the cake was the pure dextro

isomer (m.p. 98.7–99.0°) and the center of the cake still contained some of the levo isomer (m.p. 95.0–99.0°). The specific rotation of this cake was $[\alpha]_D^{25} +27.15^\circ$ in absolute ethanol. Thus, the cake contained 95.6% *d*- and 4.4% *l*-isomer. The reason that the levo isomer was still pressed in the center of the cake was that there was a 12° temperature gradient decreasing from the walls to the center of the funnel. The cake was dissolved in absolute ethanol and seeded with the pure dextro isomer (from the edge of the cake). The pure dextro form was deposited in beautiful prismatic crystals.

These crystals were used to seed the remaining 3.0-g. sample of dextro-rich Amidone dissolved in 6 ml. of absolute ethanol. Pure *d*-Amidone was deposited on standing overnight, 1.5 g., m.p. 98.7–99.0°.

The pure *d*-Amidone-*d*-acid tartrate was formed by mixing equivalents of *d*-Amidone and *d*-tartaric acid in acetone and adding a little ether, m.p. 117.8–118.1°.

SUMMARY

A method for the complete resolution of Amidone through the acid-*d*-tartrate salt is reported.

COLUMBUS 10, OHIO .

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ASYMMETRIC INDUCTION AND RACEMIZATION IN COMPOUNDS
CONTAINING THE OPTICALLY ACTIVE 2-METHYLBUTYL
(ACTIVE AMYL) RADICAL

GEORGE Y. BROKAW AND WALLACE R. BRODE

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In a continuation of induction studies in this laboratory, an attempt has been made to extend and correlate information in this field to include compounds containing the primary active amyl radical. This study of inductive effects has been directed primarily towards the induction produced in the reaction between a ketone (A) and an aliphatic Grignard reagent (B) to form a tertiary alcohol (C). Compounds (A) and (B) were chosen in such a manner that one of the two contained the optically active 2-methylbutyl (primary active amyl) radical.

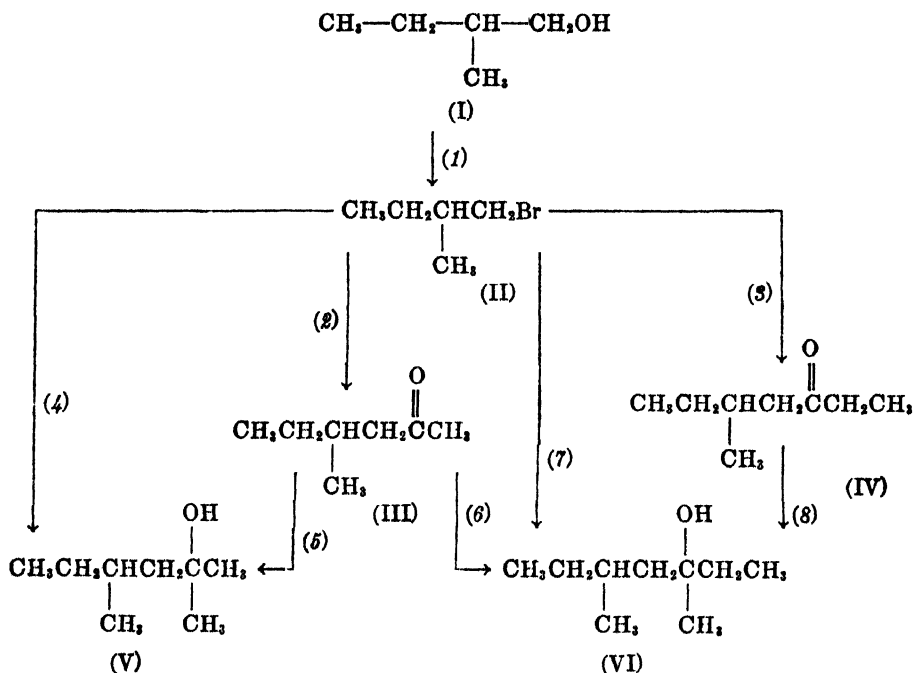


FIG. 1

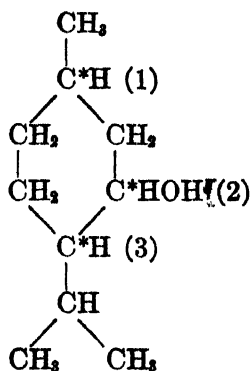
The other component was of such a nature that the resulting tertiary alcohol was 3,5-dimethyl-3-heptanol (VI), the compound for study, or 2,4-dimethyl-2-hexanol (V), the compound for reference. In certain of the procedures involved in the preparation of reagents (A) and (B) and in their interaction together, an unusual type of racemization was observed and studied.

The 2-methylbutyl radical was chosen as the optically active radical for use in this study partly because of its availability as "active amyl alcohol" (I) in

commercial fusel oil. Within this active amyl radical, the separation of the hydroxyl group and asymmetric center by the methylene structure permitted reaction upon the functional group without occurrence of Walden inversion or racemization by commonly accepted mechanisms.

By comparison of the above formulas and examination of the series of reactions in Fig. 1, it may be shown that carbon atom 2 in compound (I), carbon atom 4 in compound (V), and carbon atom 5 in compound (VI) are of identical configuration. The object of this study has been to determine the effect of the presence of this active center upon the configuration assumed by carbon atom 3 in compound (VI).

Recent investigations in the field of asymmetric induction have shown that the order of introduction of asymmetric centers may markedly influence the configuration produced. Hass and his co-workers (1) in attempting to synthesize *dl*-menthol (VII), partially reduced thymol to menthone, thus introducing asymmetric centers (1) and (3). Subsequent reduction of the menthone resulted in a considerable amount of the undesired diastereoisomer, *dl*-neomenthol. Brode and Van Dolah (2) in a recent study have shown that reversal of the order of creation of the asymmetric centers resulted in *dl*-menthol with only small amounts of *dl*-neomenthol present. No isomenthol or neoisomenthol was observed in the product. This reversal was effected by hydrogenation of thymol over copper-copper chromite, in which instance it is known that asymmetric centers (2) and (3) are the first to be introduced.



VII. Menthol

Among the reactions described in the chemical literature, involving optically active materials, that between a ketone and an aliphatic Grignard reagent to give a tertiary alcohol has been thoroughly investigated. Three approaches have been considered: (a) the reaction of an optically inactive ketone with an optically active solvent; (b) the reaction of an optically inactive ketone with an optically active Grignard reagent; and (c) the reaction of an optically active ketone with an optically inactive Grignard reagent. The first approach has met with negative results when applied to the type of reaction indicated above. The latter two approaches have previously met with some success, and both were considered in this study.

McKenzie and his co-workers (3) investigated some thirty reactions of α -ketonic esters of optically active alcohols with aliphatic and aromatic Grignard reagents. In each case the resulting α -hydroxy acid, after saponification, exhibited partial activity (usually in the order of 2-5%).

An important development was outlined by Roger (4) and further interpreted by Partridge (5) when they showed that in a reaction illustrative of approach (c), inverse order of introduction of substituents to the new center, when the inductive effect is sufficient, results in oppositely induced configuration. This result is a basis for one of the conclusions drawn from data obtained herein. Roger reacted optically active benzoin with ethylmagnesium bromide, and the optically active ethyl analog of benzoin (known to be of identical configuration) with phenylmagnesium bromide, obtaining diastereoisomeric ethylhydrobenzoin. Upon subsequent oxidation, the enantiomorphous forms of ethylbenzoin were produced.

TABLE I
3,5-DIMETHYL-3-HEPTANOL

	REACTION (6)		REACTION (7)		REACTION (8)	
	Trial (1)	Trial (2)	Trial (1)	Trial (2)	Trial (1)	Trial (2)
<i>b.p.</i> (35 mm.)	88.4-88.6	88.1-88.1	88.6-88.9	87.4-87.9	88.7-90.0	88.0-88.0
<i>n_D</i>	1.4317 ²⁴	1.4360 ¹⁵	1.4298 ^{24.2}	1.4324 ²⁵	1.4315 ^{24.3}	1.4356 ¹⁵
<i>d</i>	0.833 ²⁴	0.833 ²⁵	0.834 ²⁴	0.831 ²⁵	0.837 ²⁴	0.830 ²⁵
<i>M</i> ₄₇₀ ^o	—	+10.46	—	+9.91	+10.59	+10.28
<i>M</i> ₅₃₀ ^o	—	+8.04	—	+7.54	+8.10	+7.87
<i>M</i> ₅₈₀ ^o	6.49	+6.44	+5.99	+5.97	+4.46	+6.34
<i>M</i> ₆₅₀ ^o	—	+5.29	—	+5.06	+5.37	+5.21
<i>M</i> ₄₇₀ / <i>M</i> ₆₅₀	—	1.98	—	1.96	1.97	1.97

* The listed values for *M*₅₈₀ are 48.0% (or less) of that which they would have been had bromide (II) been the optically pure dextrorotatory form.

EXPERIMENTAL

The series of reactions outlined in Fig. 1 were employed in this investigation, rotatory dispersions being obtained for each compound listed.

d(-)-2-Methyl-1-butanol (I), (*b.p.* 129°, *n*_D²⁰ 1.4102, *d*₄²⁵ 0.819, *M*₄₇₀²⁰ -8.27, *M*₅₃₀²⁰ -6.32, *M*₅₈₀²⁰ -5.05, *M*₆₅₀²⁰ -4.17): This optically active amyl alcohol was obtained by fractionation of fusel oils containing 10-22% of the desired alcohol. Columns with efficiencies near or in excess of 100 plates are essential to prevent this fractionation from being a long and very tedious process, since the isomeric isoamyl alcohol present boiled only 3° above the active component.

d(+)-2-Methyl-1-bromobutane (II), (*b.p.* 71.04-71.7° at 150 mm., *n*_D²⁰ 1.4455, *d*₄²⁰ 1.225, *M*₄₇₀²⁰ +4.43, *M*₅₃₀²⁰ +3.57, *M*₅₈₀²⁰ +2.94, *M*₆₅₀²⁰ +2.36): Bromination of (I) with PBr₃ resulted in compound (II). This bromide was observed to undergo racemization and rearrangement, resulting in *dl*-2-methyl-1-bromobutane and 2-methyl-2-bromobutane respectively, if the work-up procedure of Brauns (6) was not followed, and if the fractionation was not carried out at reduced pressure. The rotations listed above were obtained for partially racemized bromide which was employed in the induction study, and correspond to 48.0% of the values for the pure dextrorotatory isomer as obtained by Brauns and confirmed here.

The pure primary active bromide was relatively stable, both rearrangement and racemization being induced by heat and continuing thereafter at room temperature. Hydrobromic acid catalyzed racemization and inhibited rearrangement. Sodium acetate inhibited both rearrangement and racemization.

TABLE II
2,4-DIMETHYL-2-HEXANOL

	REACTION (4)		REACTION (5) Trial (1)	LITERATURE
	Trial (1)	Trial (2)		
<i>b.p.</i> (40 mm.)	77.0-77.4	76.4-77.0	76.9-77.0	64 @ 20 mm.
n_D	1.4233 ²⁴	1.4250 ²⁰	1.4250 ²⁰	—
<i>d</i>	0.827 ²⁴	0.818 ²⁰	0.820	—
M_{470}°	+9.84	+10.24	—	—
M_{550}°	+7.51	+7.89	—	—
M_{589}°	+6.07	+6.21	+6.71	—
M_{650}°	+4.93	+5.26	—	—
M_{470}/M_{650}	1.99	1.95	—	—

* The listed values for M_{589} are 48.0% (or less) of that which they would have been had bromide (II) been the optically pure dextrorotatory form.

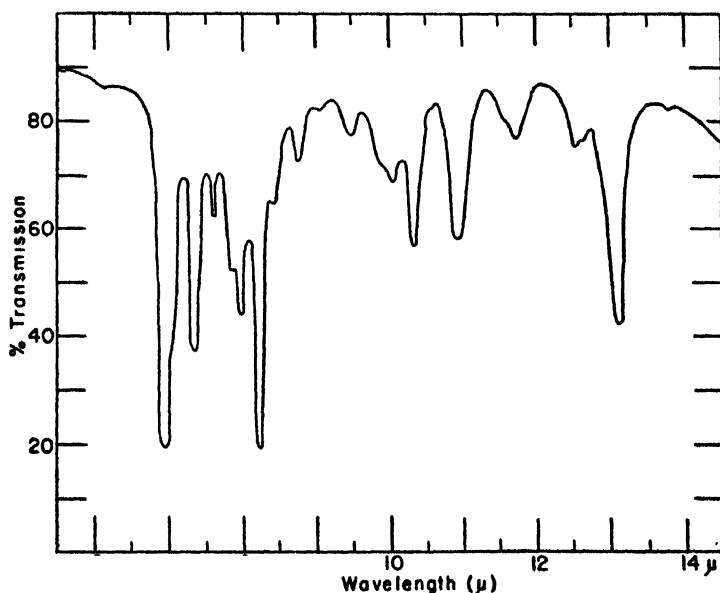


FIG. 2. INFRARED ABSORPTION SPECTRUM OF 1-BROMO-2-METHYLBUTANE

d-(+)-4-Methyl-2-hexanone (III), (b.p. 137.0-138.0°), and *d*(+)-5-methyl-3-heptanone (IV), (b.p. 157.0-158.0°): These ketones were prepared in excellent yield by the method of Newman and Booth (7), adding the Grignard reagent from (II) to the appropriate anhydride at -80°.

3,5-Dimethyl-3-heptanol (VI), (see Table I): Nearly identical rotation was observed for this alcohol when prepared from either ketone (III) or ketone (IV). When prepared directly from bromide (II), the alcohol (VI) had a somewhat lower rotation.

2,4-Dimethyl-2-hexanol (V), (see Table II): As in the case of (VI), this alcohol also had a lower rotation when prepared directly from bromide (II) than when prepared from ketone (III).

An infrared investigation of certain C_8 compounds was undertaken to determine the extent of racemization and of rearrangement. *d*(+)-2-Methyl-1-bromobutane (Fig. 2) and 2-methyl-2-bromobutane (Fig. 3) were included among these compounds. The partially racemic primary bromide displays an absorption identical with that in Fig. 2. The tertiary bromide was found to have absorption maxima at 8.9 and 12.6 μ which were applicable for analysis. A measurement of the absorption of these peaks provided an estimation of the amount of tertiary bromide present. The rotatory power was an indication of the amount of *d*(+) primary bromide present. The remainder was *dl* primary bromide.

A mixture of known composition (by the method shown above) was refluxed with hydrobromic acid, sodium acetate, and by itself. The composition of each resultant mixture

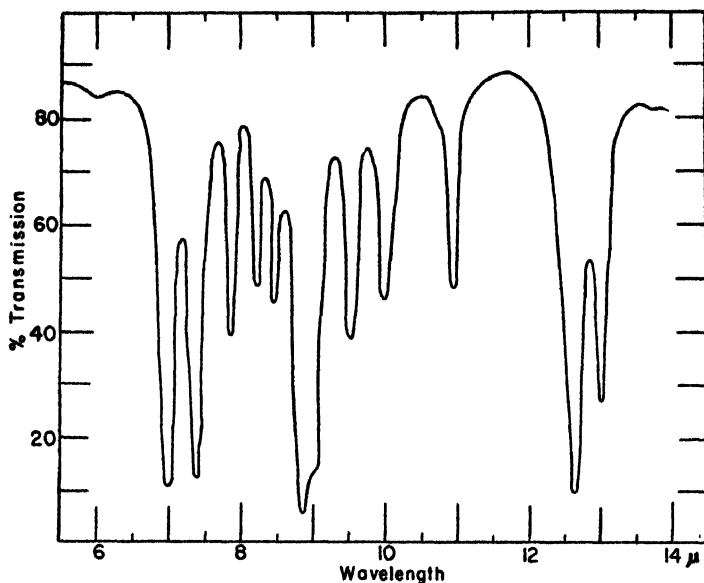


FIG. 3. INFRARED ABSORPTION SPECTRUM OF TERTIARY AMYL BROMIDE

was used to determine the relative amounts of racemization or rearrangement which had occurred.

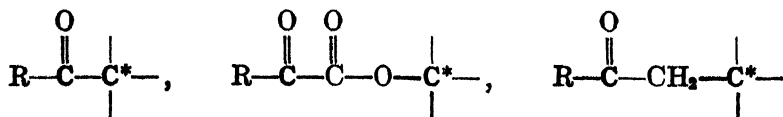
CONCLUSIONS

3,5-Dimethyl-3-heptanol was identical when prepared from either ketone (III or IV). This proved that inverse order of introduction of substituents to the new center resulted in identical configuration at that new center. In retrospect to the work of Roger and the interpretation of Partridge, it is reasonable to conclude that the ketones, in the reactions considered, exerted negligible influence toward preferential assumption of configuration at the new center.

When prepared directly from bromide (II), 3,5-dimethyl-3-heptanol (VI) showed a lower rotation than when prepared from ketones (III) and (IV). However, 2,4-dimethyl-2-hexanol (V), showed the same difference in rotation when prepared by the same two procedures. Since no second asymmetric center exists in (V), the difference must be ascribed to partial racemization of the op-

tically active center originally present. The difference noted for (VI), being analogous with respect to sign and order of magnitude, is therefore assumed to be due to the same effect.

The lack of inductive effect noted herein was correlated with results of Roger and of McKenzie to provide an interpretation of transmission or insulation of inductive power from directing center (C) to reaction center (C=O). The following structures are listed in decreasing ability to transmit this influence:



It is acknowledged that the compounds illustrating previous work possess structures permitting a coordination with the Grignard reagent. Since this might easily affect this last named conclusion, a projected program is planned to prove whether or not the methylene insulation is effective, such structures being present.

Both racemization and rearrangement of *d*(+)-1-bromo-2-methylbutane were initiated by heat but continued thereafter at room temperature. Variations in preparation of this bromide indicated that heat was the primary factor in initiating the deterioration of the optically active material.

The use of infrared absorption techniques was essential in determining the purity of the bromide (II) used for the induction study, as well as providing the only suitable method for investigation of the observed racemization and rearrangement. The absorption spectra for pure primary active amyl bromide ($M_D^{25} + 6.09$) (which is identical with that for the partially racemized bromide employed in the induction study) and for pure tertiary amyl bromide (the rearranged product) are presented in Figs. 2 and 3.

SUMMARY

The primary active amyl radical, when present as a part of the reagent molecules, has been shown to exert very little, if any, effect upon the configuration assumed by the new asymmetric center arising from the addition of a Grignard reagent to an unsymmetrical ketone.

The racemization (heretofore suspected, but never proved) and rearrangement of *d*(+)-2-methyl-1-bromobutane has been briefly studied. Two of the infrared curves used in this study are presented.

COLUMBUS, 10, OHIO

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THE RELATION BETWEEN THE ABSORPTION SPECTRA AND THE
CHEMICAL CONSTITUTION OF DYES. XXI. SOME EFFECTS
OF NON-COPLANARITY ON THE ABSORPTION SPECTRA OF
UNSYMMETRICAL DISAZO BENZIDINE DYES.

WALLACE R. BRODE AND ROBERT J. MORRIS¹

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In an earlier paper in this series Brode and Piper (1) have studied the effect of the separation of chromophores for a number of unsymmetrical disazo dyes, and have noted that the introduction of a methylene or ethylene link in such unsymmetrical dyes produced the same effect as was evident for the symmetrical dye structures; namely, that each chromophore in a single dye structure acts independently. In a preceding paper in this series (2) a study of the effects on induced non-coplanarity on the absorption spectra of a number of symmetrical disazo benzidine dyes was reported. This study revealed that the establishment of non-coplanar conditions for the benzidine nucleus caused an insulation of the two chromophores involved in the disazo molecule, permitting each half-structure to show an independent absorption. In the present paper an investigation of the absorption characteristics for a series of unsymmetrical benzidine dyes has been completed. Because of the easily resolvable absorption bands resulting from the significantly different half-structures obtained for molecules of this kind, a further investigation of the restriction to molecular resonance appearing at the 1,1'-bond in the benzidine nucleus was possible.

EXPERIMENTAL

The dyes for this study, when used for the proof of the addition of absorption curves, were synthesized from intermediates of known purity. However, in order to include a greater variety of similar structures in this investigation, absorption studies on a number of commercial dye samples were prepared. In all cases the dyes were carefully purified and analyzed before absorption measurements were taken.

The general methods available for the preparation of disazo dyes by tetrazotization and coupling were employed. The commercial dyes were examined for shading agents and salt content before further purification (3). All the dyes were then converted to their corresponding di-*o*-tolylguanidine salts for continued purification, analysis, and absorption studies. This conversion not only served in further elimination of undesirable organic and inorganic impurities but also increased their spirit solubility by destroying the water-solubilizing properties of the strongly acid groups present.

Since the absorption studies were made using the dyes in their di-*o*-tolylguanidine salt modifications, extensive comparisons of the absorption spectra for these salts with their corresponding sodium salts were made. These comparisons indicated that the only variation not attributable to the necessity of using different solvent systems occurred between 220 and 240 m μ . This was probably due to the absorption of the di-*o*-tolylguanidine constituent. However, since the absorption characteristics for this region were relatively unimportant to the data presented, the agreement was considered sufficient to allow conclusions to be drawn on the absorption spectra for these dye salts.

¹ Present address, University of Nevada, Reno, Nevada.

All the dyes after suitable purification were analyzed for purity by use of a standardized titanium trichloride solution. Corrections to 100% purity on the basis of these determinations were applied to all absorption spectra taken.

The absorption measurements were made by the use of a Beckman quartz spectrophotometer. The properly diluted samples were introduced into a 1.00-centimeter silica cell and absorption curves measured against a comparison solvent. A dilution to 0.000015 *M* served for obtaining the complete absorption spectra on all the dyes. In neutral solution this concentration was attained by the proper dilution of a 0.00006 *M* alcoholic stock solution of the dye with more 95% ethanol. For measurements in basic media, dilution to a final concentration of 0.000015 *M* was attained by the dilution of the 0.00006 *M* stock with aqueous sodium hydroxide. Determinations in concentrated acid media were made by dilution of the stock solution to 0.000015 *M* with 12 *N* HCl. Absorption spectra, after correction to one hundred per cent purity, were recorded with molecular extinction as ordinates and frequency (fresnels) as abscissa.

DISCUSSION OF RESULTS

In the classification of complex structures exhibited by dye molecules, it has been shown that a consistent multiple frequency effect was evident in their absorption spectra. Investigations of this nature (4) have clearly indicated that a definite correlation between the calculated and observed positions of absorption band maxima exists and that the calculated positions may be located by assuming them to be small whole number multiples of a fundamental frequency for a given dye structure. In this investigation this correlation was found to be very useful for permitting a satisfactory classification of the observed absorption spectra when applied to a series of unsymmetrical benzidine dyes. The absorption curves of the azo dyes reported in Table I can be satisfactorily interpreted on a frequency basis by assigning a fundamental frequency for the observed band system of each dye investigated. The observed absorption peaks agree closely in number and position to those that may be calculated. Furthermore, each of the unsymmetrical polyazo dyes listed in the Table require the assumption of two fundamental frequencies for a proper interpretation of the observed maxima, indicating that their absorption was characteristic of a summation of the band systems for each of the two partially insulated chromophores, assuming a non-coplanar configuration for the benzidine nuclei involved. Examples of the absorption spectra evident for structures of this kind may be observed in Figure 1.

Although a partial restriction to complete molecular conjugation appears at the 1,1'-(diphenyl) bond in the benzidine nucleus, there is still evidence of conjugation through this bond as observed in the absorption spectra. This is shown in Figure 2 by the comparison of the absorption spectra of the disazo dye (A) with the separate (C and D) and composite spectra (B) observed for its component half-structures. It may be noted from this figure that the absorption values of the band maxima of the disazo molecule are increased in intensity and shifted to lower frequency values, a characteristic property for conjugate structures.

The interpretation based on a non-coplanar configuration is further strengthened by the comparison (Figure 4) of the absorption spectra of the dye prepared

TABLE I
DATA ON THE BAND SYSTEMS OF THE DISAZO AND TRISAZO DYES (SOLVENT C_2H_5OH)
TWO BAND SYSTEMS

DYE (COLOR INDEX NO. INDICATED AS C. I. NO.)	PURITY ANALYTICAL DATA	FUNDAMENTAL FREQUENCY, (F)	LOCATION OF THE OBSERVED AND CALCULATED BAND FREQUENCIES, THE RATIO OF THE OBSERVED TO FUNDAMENTAL FREQUENCIES, AND THE EXTINCTION VALUE OF THE PEAK FOR THE PRINCIPAL BAND IN EACH BAND SYSTEM			
PART I. DISAZO DYES						
No. 1 in Figure 1	89%	A. 290f	Observed	580f	920f	
			Calculated	580(2)	870(3)	
			Molecular Extinction	40.0 × 10 ³		
		B. 395	Observed	790	1170	
			Calculated	790(2)	1185(3)	
			Molecular Extinction	42.0 × 10 ³		
No. 2 in Figure 1 (C.I. No. 431)	95%	A. 300	Observed	600	960	1200
			Calculated	600(2)	900(3)	1200(4)
			Molecular Extinction	36.0 × 10 ³		
		B. 395	Observed	790	1200	
			Calculated	790(2)	1185(3)	
			Molecular Extinction	36.0 × 10 ³		
No. 3 in Figure 1 (C.I. No. 419)	96%	A. 295	Observed	590	960	1210
			Calculated	590(2)	885(3)	1180(4)
			Molecular Extinction	37.0 × 10 ³		
		B. 395	Observed	790	1210	
			Calculated	790(2)	1185(3)	
			Molecular Extinction	43.0 × 10 ³		
No. 8 in Figure 4	88%	A. 300	Observed	600	910	
			Calculated	600(2)	900(3)	
			Molecular Extinction	31.0 × 10 ³		
		B. 420	Observed	840	1210	
			Calculated	840(2)	1260(3)	
			Molecular Extinction	44.0 × 10 ³		
PART II. TRISAZO DYES						
C. I. No. 581	72%	A. 250	Observed	500	750	
			Calculated	500(2)	750(3)	
			Molecular Extinction	48.0 × 10 ³		
		B. 310	Observed	620	940	
			Calculated	620(2)	930(3)	
			Molecular Extinction	33.0 × 10 ³		

TABLE I—*Continued*

DYE (COLOR INDEX NO. INDICATED AS C. I. NO.)	PURITY ANALYTICAL DATA	FUNDAMENTAL FREQUENCY, (F)	LOCATION OF THE OBSERVED AND CALCULATED BAND FREQUENCIES, THE RATIO OF THE OBSERVED TO FUNDAMENTAL FREQUENCIES, AND THE EXTINCTION VALUE OF THE PEAK FOR THE PRINCIPAL BAND IN EACH BAND SYSTEM			
PART II. TRISAZO DYES—Continued						
C. I. No. 582	73%	A. 250	Observed	500	750	
			Calculated	500(2)	750(3)	
			Molecular Extinction	50.0 × 10 ³		
		B. 315	Observed	630	940	
			Calculated	630(2)	945(3)	
			Molecular Extinction	34.0 × 10 ³		
C. I. No. 593	74%	A. 230	Observed	460	680	900
			Calculated	460(2)	690(3)	920(4)
			Molecular Extinction	61.0 × 10 ³		
		B. 390	Observed	780	1180	
			Calculated	780(2)	1170(3)	
			Molecular Extinction	42.0 × 10 ³		
C. I. No. 594	75%	A. 230	Observed	460	680	930
			Calculated	460(2)	690(3)	920(4)
			Molecular Extinction	58.0 × 10 ³		
		B. 400	Observed	800	1180	
			Calculated	800(2)	1200(3)	
			Molecular Extinction	58.0 × 10 ³		

from the unsubstituted benzidine nucleus (No. 1) with the 2,2'-dimethyl derivative (No. 8). In this case, the substitution reduced the intensity of the low frequency absorption band and shifted it to a higher frequency, causing it to conform more nearly with the absorption contour of the composite half-structures. The disazo dye prepared from the 2,2',6,6'-tetramethylbenzidine nucleus showed absorption maxima of the principal bands which closely agree with those shown for a composite of the component half-structures. However, as this dye, due to some difficulties in preparation, was considered somewhat impure, its absorption spectra was not reproduced.

Studies made in acid and basic media support the contention that non-coplanarity is present in these dye molecules. With the establishment of more polar conditions for the molecule either by the use of a solvent that would favor the establishment of the quinoid form (Figures 3, 5, and 6) or by introducing the more polar methoxyl groups into the benzidine nucleus in the 3,3'-position (Figure 4, Dye No. 7), the partial restriction previously observed for dyes containing the unsubstituted benzidine nucleus either vanishes or is greatly

reduced. This becomes evident when the absorption spectra for the dye molecules altered in the above manner are examined. Close scrutiny reveals that the absorption maxima for these compounds no longer conform to two principal band systems, but may be analyzed by a single system. Therefore, dyes altered

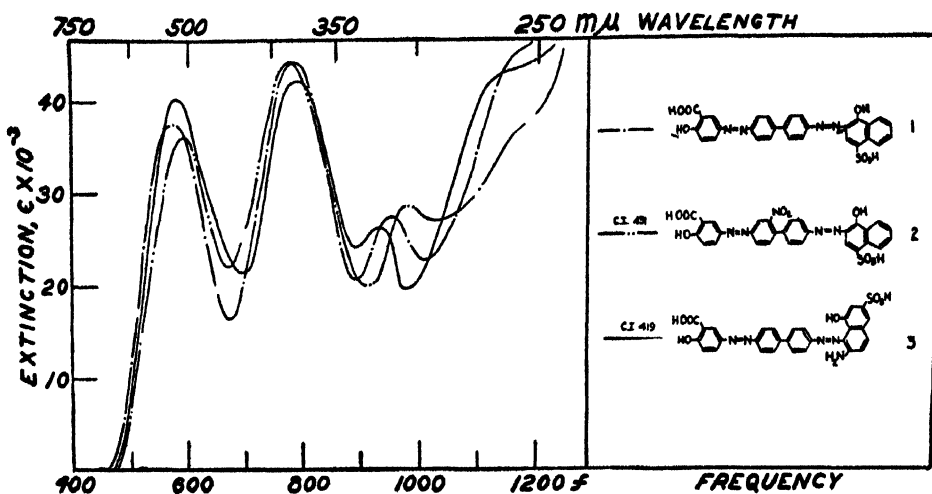


FIG. 1. THE ABSORPTION SPECTRA OF THREE UNSYMMETRICAL DISAZO DYES (IN 95% ETHANOL). (SEE TABLE I)

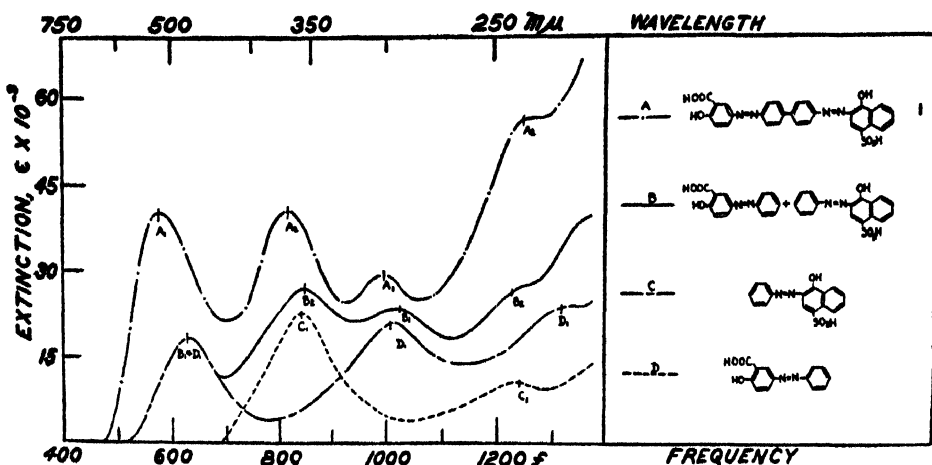


FIG. 2. THE ABSORPTION SPECTRA OF AN UNSYMMETRICAL DISAZO DYE COMPARED WITH THE ABSORPTION OF ITS HALF-STRUCTURES AND ITS COMPOSITE (IN 95% ETHANOL).

in this respect show no evident restriction to molecular resonance at the 1,1'-bond, resulting in a more complete molecular conjugation, with the molecular extinction values for the principal band greatly increased and the resulting band shifted to a lower frequency.

In Table I are given data on examples of some of the dyes studied and the

analysis of the observed band frequencies into multiple frequency systems characteristic of the separated resonance forms. Frequency data are given in fresnel units (vibrations per second $\times 10^{-12}$). The first four examples are of unsymmetrical disazo dyes in which restriction at the 1,1'-diphenyl linkage has induced

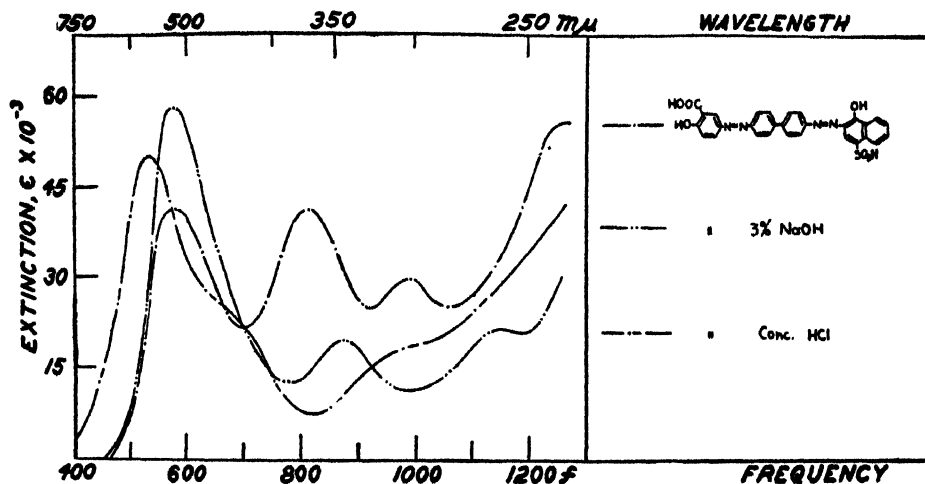


FIG. 3. A COMPARISON OF THE ABSORPTION SPECTRA OF AN UNSYMMETRICAL DISAZO BENZIDINE DYE IN 95% ETHANOL, 3% SODIUM HYDROXIDE AND 12 N HYDROCHLORIC ACID.

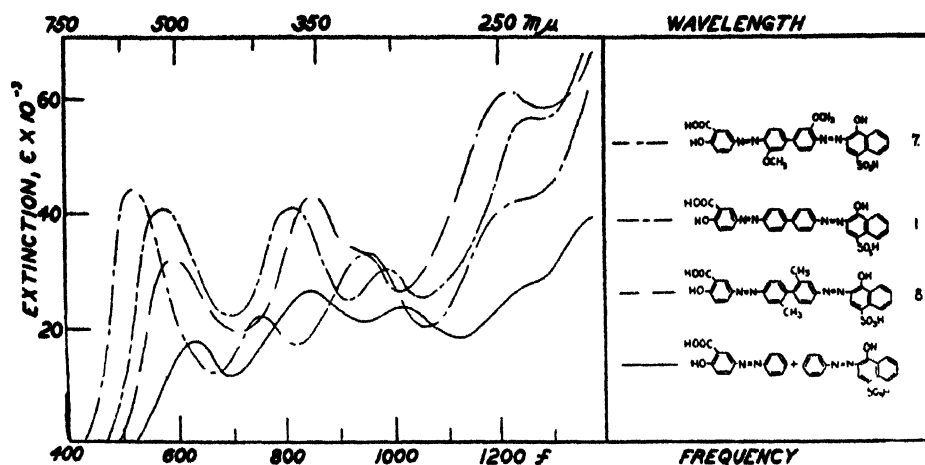


FIG. 4. A COMPARISON OF THE ABSORPTION SPECTRA OF CERTAIN UNSYMMETRICAL DISAZO BENZIDINE DYES WITH AN APPROPRIATE COMPOSITE OF THEIR HALF-STRUCTURES

separate systems corresponding to the addition of the two different component monoazo parts (see also Figures 1, 2, and 3). The separate systems are indicated by A and B in the Table and correspond to the frequency system of the monoazo component dyes (Figure 2).

The second part of Table I gives examples of some trisazo dyes in which

the absorption spectra curves are resolvable into two multiple series of band systems indicating a restriction within the molecule so as to produce separate resonance systems.

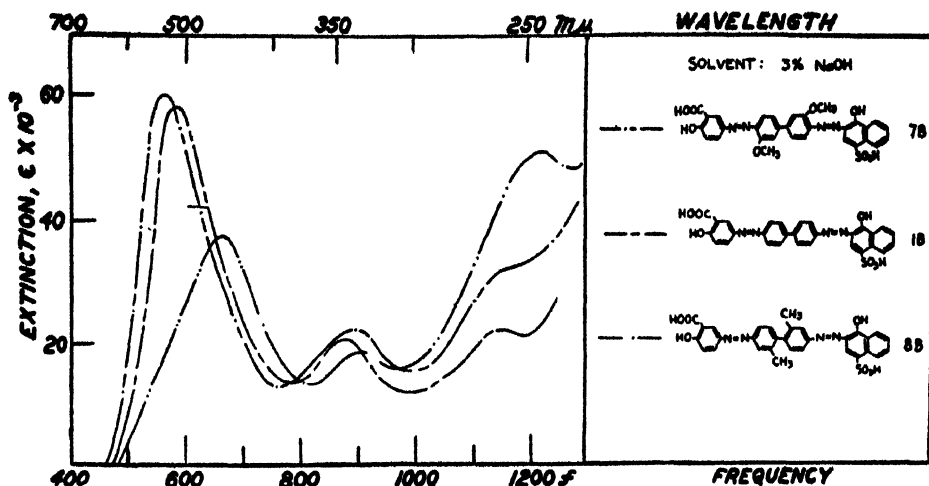


FIG. 5. THE ABSORPTION SPECTRA OF THREE TYPICAL UNSYMMETRICAL DIAZO DYES IN BASIC MEDIA

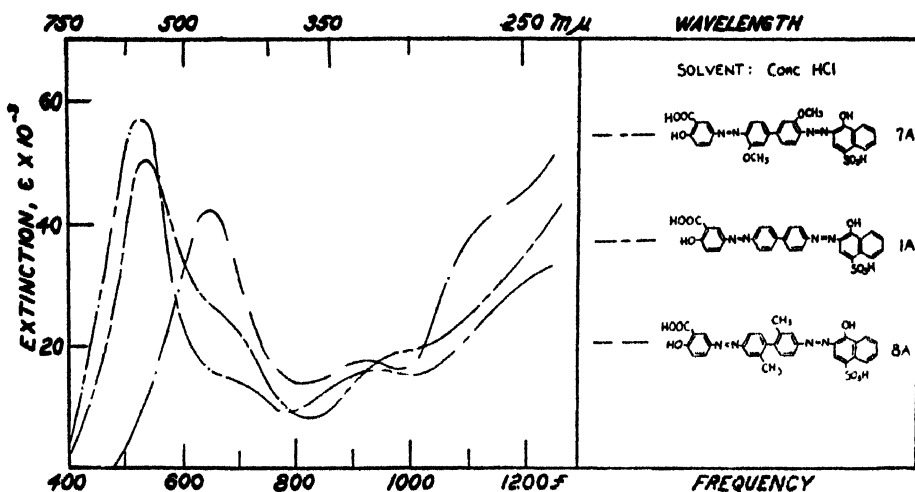
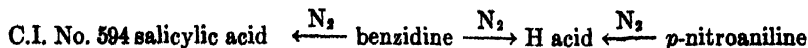
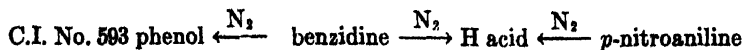
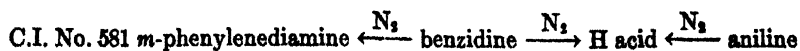


FIG. 6. THE ABSORPTION SPECTRA OF THREE TYPICAL UNSYMMETRICAL DYES IN CONCENTRATED ACIDIC MEDIA

The similarity of the trisazo dye absorption spectra with the composite curves of the addition of the absorption curves of the disazo H acid dye and monoazo residue corresponding to cleavage of the trisazo dye at the 1,1'-diphenyl linkage indicates an induced non-coplanarity and separation of the resonance system at this linkage.

The structure of these trisazo dyes may be indicated as:



SUMMARY

An interpretation of the absorption spectra for twelve dis- and tris-azo benzidine dyes has been prepared. The absorption spectra of a series of disazo benzidine dyes and the suitable half-structures has been recorded. These data indicate that the partial restriction evident in the unsubstituted benzidine nucleus is either removed or greatly reduced by increasing the polarity of the dye structures. Increased insulation at the 1,1'-(diphenyl) bond appears when non-coplanarity of the benzidine nucleus is induced by the substitution of methyl groups in the 2,2'- and the 2,2',6,6'-positions.

COLUMBUS, OHIO

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COMPLEX FORMATION BETWEEN ALLYL ALCOHOL AND CUPROUS CHLORIDE

RICHARD E. KEPNER AND LAWRENCE J. ANDREWS

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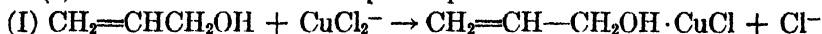
The tendency for certain olefins to form coordination complexes with cuprous salts has been amply demonstrated. In the cases of butadiene, isoprene, and piperylene the formulas of the complexes with cuprous chloride have actually been established as diene·2CuCl (1, 2).

Cuprous chloride is known to promote the conversion of allyl alcohol to allyl chloride in concentrated hydrochloric acid solution (3, 4). The catalytic effect of CuCl₂⁻ in promoting the hydrolysis of allyl chloride and other allylic halides has also been described (5, 6). It has been presumed that the catalytic effect of cuprous salts in these reactions results from the formation of complexes with the allylic compounds (6, 7).

With these facts in mind an investigation of the tendency for complex formation between cuprous chloride or CuCl₂⁻ with allyl alcohol in aqueous solution has been undertaken. It has been demonstrated that an equilibrium exists between the alcohol, the cuprous salts and CH₂=CHCH₂OH·CuCl.

Qualitative experiment showed that cuprous chloride is soluble in allyl alcohol to a considerable extent. The resulting solution is water-soluble but when treated with ether or carbon tetrachloride reprecipitates cuprous chloride. These observations suggested that a water-soluble olefin-cuprous complex had formed.

A procedure similar to that used for studying complex formation between olefins and silver ion (8) was adopted for investigating the reaction between allyl alcohol and CuCl₂⁻. In experiments in which allyl alcohol was distributed between carbon tetrachloride and aqueous solutions of hydrochloric acid containing dissolved cuprous chloride it was observed that the total olefin content of the aqueous layer increased with increasing concentration of cuprous salts. From two series of runs (at 1.1 and 2.2 *M* hydrochloric acid concentration in the aqueous layer) data were obtained and interpreted on the assumption that the equilibrium (I) was established in the aqueous phase.



Equilibrium constants, *K*₁, for this reaction were calculated from the expressions

$$K_1 = \frac{(A_w - A')(Cl^-)}{(A')(CuCl_2^-)} = \frac{(A_w - A')(Cl^-)}{(A') \frac{(Cu_t - A_w + A')}{1 + K_0(Cl^-)}}$$

in which

A' = *K*₀*A*₀ = the concentration of uncomplexed allyl alcohol in the aqueous phase in moles per liter

*K*₀ = the distribution coefficient of allyl alcohol between carbon tetrachloride and aqueous hydrochloric acid

A_c = the concentration of allyl alcohol in the carbon tetrachloride phase in moles per liter

A_w = the total allyl alcohol concentration in the aqueous phase in moles per liter

Cu_t = the original cuprous salt concentration in the aqueous phase in moles per liter

$$K_c = \frac{(CuCl_3^-)}{(CuCl_2^-)(Cl^-)} = 0.31$$

Since hydrochloric acid solutions of cuprous chloride contain $CuCl_3^-$ in addition to $CuCl_2^-$, the term K_c is introduced to determine the $CuCl_3^-$ concentration at equilibrium. The value for K_c was calculated from the known constants K_a and K_b (9, 10).

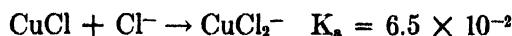


TABLE I

DISTRIBUTION RATIO OF ALLYL ALCOHOL BETWEEN CARBON TETRACHLORIDE AND AQUEOUS SOLUTIONS AT 25°

ELECTROLYTE IN AQUEOUS PHASE	MAGNITUDE OF A_c MOLE/LITER	K_d
1.14 M HCl	0.01-0.035	14.8
2.28 M HCl	.01	14.2
none	.01	15.9
0.10 M NaCl		
2.28 M HCl	.01	13.9

Values of K_d , the distribution coefficient of allyl alcohol between carbon tetrachloride and aqueous hydrochloric acid at 25°, are listed in Table I. The coefficient obtained for the run in which sodium chloride was added to the aqueous layer demonstrates the salting out of allyl alcohol from the aqueous phase by other than a cuprous halide.

The equilibrium data for the distribution experiments in the presence of dissolved cuprous chloride are listed in Table II. In actual practice the hydrochloric acid concentrations in the aqueous phase, neglecting the dissolved cuprous salt, were 1.14 M or 2.28 M. To account for the consumption of chloride ion in forming complexes with cuprous chloride the values 1.1 M or 2.2 M were used as close approximations for chloride ion concentration in calculating K_i values.

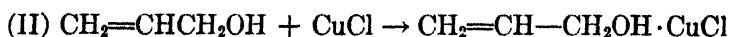
The several K_i values obtained are in reasonable agreement with each other. Since the approximations as to chloride ion concentration and the assumptions that the activity coefficients of anions are all unity are undoubtedly in error, the expected accuracy of K_i values is not too great. Other errors result from the limited accuracy of K_a and K_b values and from inclusion of traces of oxygen in the reaction vessel.

As a check on the validity of the assumption that the distribution data could be explained on the basis of formation of $\text{CH}_2=\text{CHCH}_2\text{OH} \cdot \text{CuCl}$, a series of solubility measurements of solid cuprous chloride in aqueous allyl alcohol solutions was made. The solutions were analyzed for cuprous compounds after the

TABLE II
DISTRIBUTION OF ALLYL ALCOHOL BETWEEN CARBON TETRACHLORIDE AND AQUEOUS HYDROCHLORIC ACID SOLUTIONS OF CUPROUS CHLORIDE AT 25°

A_0 MOLE/LITER	A_w MOLE/LITER	Cu_2 MOLE/LITER	K_1
(Cl ⁻) = 1.1 M			
0.01056	0.1814	0.0411	15.1
.01040	.1830	.0460	16.3
.00966	.1904	.0788	15.5
.01014	.1856	.0627	12.8
.00936	.1934	.0929	15.3
.01364	.2654	.0893	17.9
Av.....			15.5
(Cl ⁻) = 2.2 M			
.01088	.1846	.0797	15.0
.01086	.1848	.0736	17.3
.01142	.1792	.0402	17.1
.01022	.1912	.1093	18.7
Av.....			17.0

solid and liquid phases had reached equilibrium. Equilibrium constants for reaction (II) were calculated.



from the expression

$$K_{II} = \frac{(\text{Cu}^+)}{(A - \text{Cu}^+)}$$

in which

Cu^+ = concentration of soluble cuprous compounds in moles per liter

A = original allyl alcohol concentration of aqueous solution in moles per liter

All determined cuprous concentrations were corrected on the basis of blank runs on the solubility of cuprous chloride in the alcohol free solvent.

Three series of solubility measurements were made. In the first series using neutral aqueous solutions of allyl alcohol considerable hydrolysis of cuprous chloride occurred as evidenced by development of a brick red color in the solid

phase. In the other two series, run in solutions originally 0.01 *M* with respect to hydrochloric acid, no hydrolysis was observed. The data for the several runs are summarized in Table III. The small amount of CuCl_2^- introduced in the acidic media should be insufficient to affect the results within the limits of error. The discrepancy in values for K_{II} in Series II and Series I and III may result from errors in determining the solubility of cuprous chloride in the solvent. The

TABLE III
SOLUBILITY OF CUPROUS CHLORIDE IN AQUEOUS ALLYL ALCOHOL SOLUTIONS AT 25°

A MOLE/LITER	Cu^+ FOUND MOLE/LITER	Cu^+ CORRECTED MOLE/LITER	K_{II}
SERIES I (HCl) ORIG. = 0.000 <i>M</i>			
0.0145	0.00778	0.00540	(0.59)
.0290	.0137	.0113	.64
.0580	.0256	.0232	.67
.0724	.0300	.0276	.62
.1086	.0459	.0435	.67
.0000	.00238	—	—
Av.			0.65
SERIES II (HCl) ORIG. = 0.0094 <i>M</i>			
0.0132	0.00782	0.00684	(1.07)
.0264	.0125	.0115	0.77
.0527	.0246	.0236	.81
.0658	.0298	.0288	.78
.0986	.0438	.0428	.77
.0000	.00098	—	—
Av.			0.78
SERIES III (HCl) ORIG. = 0.0094 <i>M</i>			
0.9923	0.406	0.404	0.69
.5954	.234	.232	.64
.3969	.153	.151	.61
.0000	.0022	—	—
Av.			0.65

agreement between the three series is reasonably good and indicates that the solubility expression II holds over a wide range of alcohol concentrations.

Choosing 0.7 as an average value for K_{II} one can calculate the value for K_I by use of the data of Noyes and Chow (9).

$$K_I = \frac{K_{II}}{K_s} = \frac{0.7}{0.065} = 11$$

This figure checks those obtained from the distribution experiments reasonably well considering the limitations of the methods as previously mentioned.

Inconclusive evidence was obtained for the formation of $2\text{CH}_2=\text{CHCH}_2\text{OH} \cdot \text{CuCl}$. It was noted in a few distribution runs in which A' values ranged as high as 0.4–0.6 M that slightly more alcohol appeared to be complexed in the aqueous layer than there were moles of cuprous ion in solution. A similar observation was made in a series of runs in which the chloride ion concentration of the aqueous phase was varied and the ionic strength maintained constant throughout the series by using varying amounts of potassium chloride and potassium nitrate. At high nitrate ion concentration the amount of complexed alcohol again exceeded the total moles of cuprous compounds in solution. No satisfactory quantitative treatment for these results has been found. The possibility of higher complex formation of this type does not seem too remote in view of the evidence existing for the formation of $2\text{CH}_2=\text{CHCH}_2\text{OH} \cdot \text{Ag}^+$ (8).

The possibility that some $\text{CH}_2=\text{CHCH}_2\text{OH} \cdot \text{CuCl}_2^-$ might have formed in the distribution runs was considered. No positive evidence for its existence was found. Attempts to discover this complex by the series of experiments run at varying chloride ion concentrations as noted above were unsuccessful.

EXPERIMENTAL

Cuprous chloride. This material was prepared in 5-g. batches according to the procedure of Keller and Wycoff (11). Each batch was stored in a tightly stoppered container and used within two days after preparation.

Allyl alcohol. A sample of Paragon Testing Laboratories allyl alcohol was fractionated through a silvered vacuum jacketed, 1.5 x 120 cm. glass helix (3 mm. turns) packed column and a cut collected at 97.1°/761 mm.

Carbon tetrachloride. C. P. carbon tetrachloride was fractionated through the column described above and material boiling at 76.0°/761 mm. collected.

Solubility of cuprous chloride in pure allyl alcohol. One gram of cuprous chloride was almost completely dissolved in twenty ml. of allyl alcohol by a few minutes shaking at room temperature. The clear brown solution was decanted and investigated as follows: One sample was diluted with water to give a colorless solution. This aqueous solution after treatment with ammonium hydroxide slowly developed the color of cupric ammonia complex ion. Other samples of the allyl alcohol solution of cuprous chloride were treated with ether and with carbon tetrachloride. In both cases cuprous chloride was precipitated. This was verified by analyzing a portion of this precipitate which had been washed thoroughly with ether. A weighed sample was dissolved in hydrochloric acid and analyzed volumetrically for cuprous content in the usual manner.

Anal. Calc'd for CuCl : Cu, 64.2. Found: Cu, 62.7.

Absolute ethanol gave no evidence of acting as a solvent for cuprous chloride.

Distribution experiments. Solutions of allyl alcohol in carbon tetrachloride were brought to 25° in a constant temperature bath and standardized against bromide-bromate solution by the following modification of the procedure of Francis (12): A sample of the bromide-bromate solution (0.05 M available bromine) was pipetted into 25 ml. of water in a glass-stoppered Erlenmeyer flask; the flask was flushed with nitrogen and a 5-ml. sample of the allyl alcohol solution to be analyzed was introduced. Ten ml. of 6 N sulfuric acid was added and the tightly stoppered flask shaken mechanically for five minutes. One gram of potassium iodide was then added and the liberated iodine titrated with 0.025 N sodium thiosulfate solution.

One hundred-ml. samples of the standardized carbon tetrachloride solutions were placed

in a standard taper three-neck flask equipped with a mercury sealed stirrer and a device for flushing the system with nitrogen. The flask was immersed in a constant temperature bath at 25°. A sample of cuprous chloride was weighed into a nitrogen filled volumetric flask and dissolved by the addition of a measured volume of concentrated hydrochloric acid of known concentration. The volumetric flask was filled to the mark with freshly-boiled distilled water, (cooled to 25°) and a 10-ml. sample of this solution was immediately added to the three-neck flask against a counter current stream of nitrogen. The nitrogen stream was discontinued. The flask was closed to the atmosphere and the contents stirred vigorously for forty-five minutes. After a ten-minute interval to allow phase separation, samples of the carbon tetrachloride layer were removed for allyl alcohol analysis by the bromide-bromate procedure. Owing to the small volume of the aqueous phase, the allyl alcohol content of this layer was calculated from the initial and final concentrations of allyl alcohol in the carbon tetrachloride phase. No cuprous salts appeared to accumulate in the carbon tetrachloride layer, as shown by the complete lack of any blue copper ammonia complex formation on shaking this phase with concentrated ammonium hydroxide.

Samples of the aqueous cuprous solution were also taken immediately after its preparation for volumetric determination of the cuprous content according to the procedure of Hatch and Estes (6). It was found that the volumetric analyses agreed to within 1-1.5% of those calculated from the weight of cuprous chloride used.

Solubility of cuprous chloride in aqueous solutions of allyl alcohol. Solutions of allyl alcohol in freshly boiled distilled water were prepared and standardized by the bromide-bromate procedure. In some cases the solutions also contained dilute hydrochloric acid. To 50 ml. of each solution in a nitrogen filled glass-stoppered Erlenmeyer flask was added excess (0.5-2.5 g.) cuprous chloride. The flasks were tightly sealed and shaken mechanically for four hours at 25°. Preliminary experiments indicated that equilibrium was established after about two hours of shaking. The excess solid cuprous chloride was allowed to settle, and samples of the aqueous solution were carefully removed under a nitrogen atmosphere and analyzed immediately for cuprous content.

SUMMARY

Evidence based on distribution experiments and solubility measurements supports the conclusion that in aqueous solution allyl alcohol forms a complex of the type $\text{CH}_2=\text{CHCH}_2\text{OH} \cdot \text{CuCl}$ on treatment with cuprous chloride or CuCl_2^- . Equilibrium data for the complex formation are presented.

DAVIS, CALIFORNIA

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INVESTIGATIONS ON STEROIDS. X. REVISION OF NOMEN- CLATURE OF PREVIOUSLY DESCRIBED COMPOUNDS¹

MAXIMILIAN EHRENSTEIN

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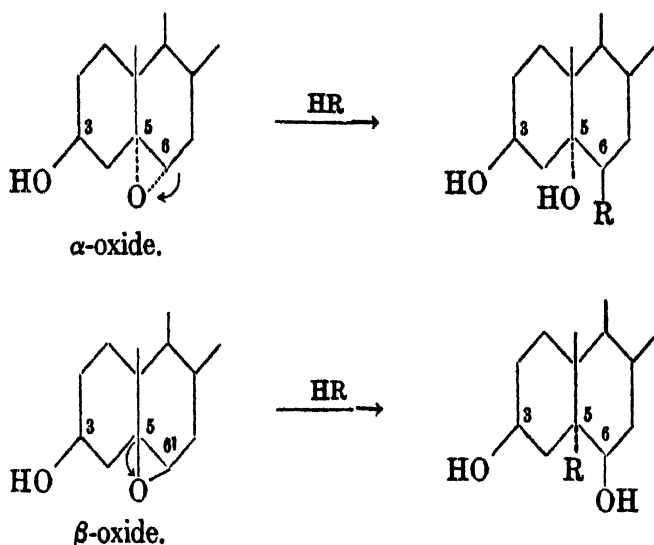
In a number of publications from this laboratory (1, 2, 3, 4, 5) various 5,6-oxides and 3,5,6-triols had been assigned arbitrary configurations at carbon atoms 5 and 6. Recent investigations performed in several laboratories, notably that of Ruzicka, now make it possible to define more accurately the configuration of these compounds. It appears that the necessary revisions are rather comprehensive.

The school of Ruzicka (6) established the configuration of the so-called α -cholesteryl oxide and of β -cholesteryl oxide. They should now be labelled 5,6(α)-oxidocholestane-3(β)-ol and 5,6(β)-oxidocoprostan-3(β)-ol respectively, designations which clearly express the configurations at both carbon atoms 5 and 6. The preceding arbitrary nomenclature was thus shown to be correct. Hattori (7) and later Baxter and Spring (8) studied the fission reactions of the two cholesteryl oxides, using water, hydrochloric acid, and glacial acetic acid. Fission of the oxide rings can also be brought about by catalytic hydrogenation (9, 9a, 10).² The opening of the oxide rings is known to be accompanied by a change of configuration at the carbon atom at which the bond with the oxygen atom is ruptured, as has been shown *e.g.* in the sugar series (lit. *cf.* 12). Applied to α or β -cholesteryl oxide such a rupture may lead in each case to two different

¹ Aided by grants from Sharp and Dohme, Inc., Philadelphia and from the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council.

² Ruzicka (11) also studied the catalytic hydrogenation of the α -oxide and β -oxide of dehydroisoandrosterone acetate [3(β)-acetoxy-5,6(α)-oxidoandrostane-17-one and 3(β)-acetoxy-5,6(β)-oxidoetiocholane-17-one respectively]. The results were analogous to those obtained with the acetates of α -cholesteryl oxide and β -cholesteryl oxide respectively (9, 9a).

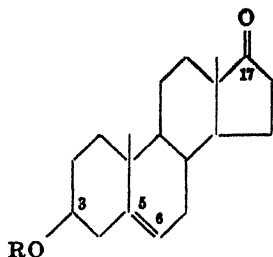
trans forms. It appears from the experiments that the one of the two possible stereoisomeric forms predominates. In each case the fission reaction leads to the predominant formation of cholestane derivatives. The equally possible coprostane derivatives are only produced in negligible amounts if at all. These reactions may be formulated in the following way ($R = H, OH, Cl, OAc$):



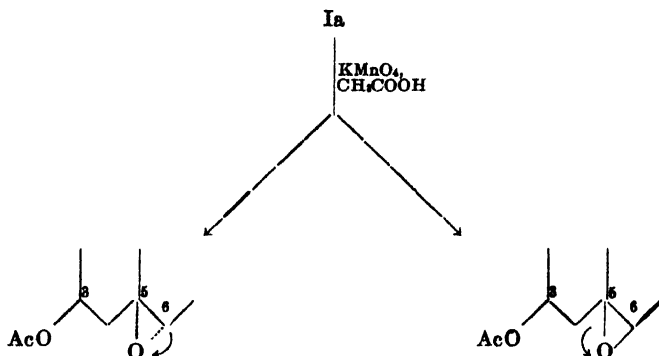
Fission of the α -oxide ring, therefore, occurs mainly at carbon atom 6 and of the β -oxide ring chiefly at carbon atom 5.

In considering some of our previous publications (1, 2, 3, 4, 5) in the light of these recent findings, it appears necessary to alter the nomenclature and the configurational formulas in many instances. The changes follow by applying the above considerations to a number of reactions described in these publications. The configurational evidence stems from the fission products of the 5,6-oxides, to which are related the other compounds of the pertinent reaction scheme. Inasmuch as the reactions concerned have been discussed before, the material will be presented by way of formula schemes. Each compound will be characterized by its new configurational formula and nomenclature to which the previous names will be added in brackets. Previous names will be marked by a reference and by the Roman numeral given to the formula in that particular publication. It is to be noted that the configuration at carbon atom 5 is expressed by the general nomenclature; hence the additional marking by Greek letters is not necessary.

The first series of reactions are derived from dehydroisoandrosterone (I):

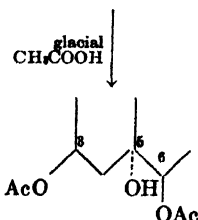


- I. R = H, Dehydroisoandrosterone.
 Ia. R = Ac, Dehydroisoandrosterone acetate.

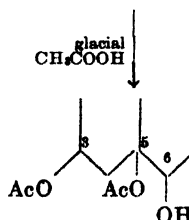


- II. 3(β)-Acetoxy-5,6(α)-oxidoandrostane-17-one. m.p. 221–222.5°; $[\alpha]_D^{25} - 10.0^\circ$
 [Androstane-(5,6)(β)-oxide-17-one-3(β)-ol acetate. (3, V b)]
 [Androstane-(5,6)(α)-oxide-17-one-3(β)-ol acetate. (4, VIII)]

- III. 3(β)-Acetoxy-5,6(β)-oxidoetiocholan-17-one. m.p. 188–190°; $[\alpha]_D^{25} + 58.4^\circ$
 [Androstane-(5,6)(α)-oxide-17-one-3(β)-ol acetate. (3, Va)]
 [Androstane-(5,6)(β)-oxide-17-one-3(β)-ol acetate. (4, IX)]



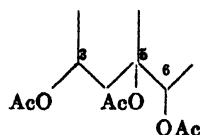
- IV. 3(β),6(β)-Diacetoxyandrostane-5-ol-17-one.
 [Androstane-17-one-3(β),5,6(trans)-triol 3,6-diacetate. (3, VIII) (4, X)]



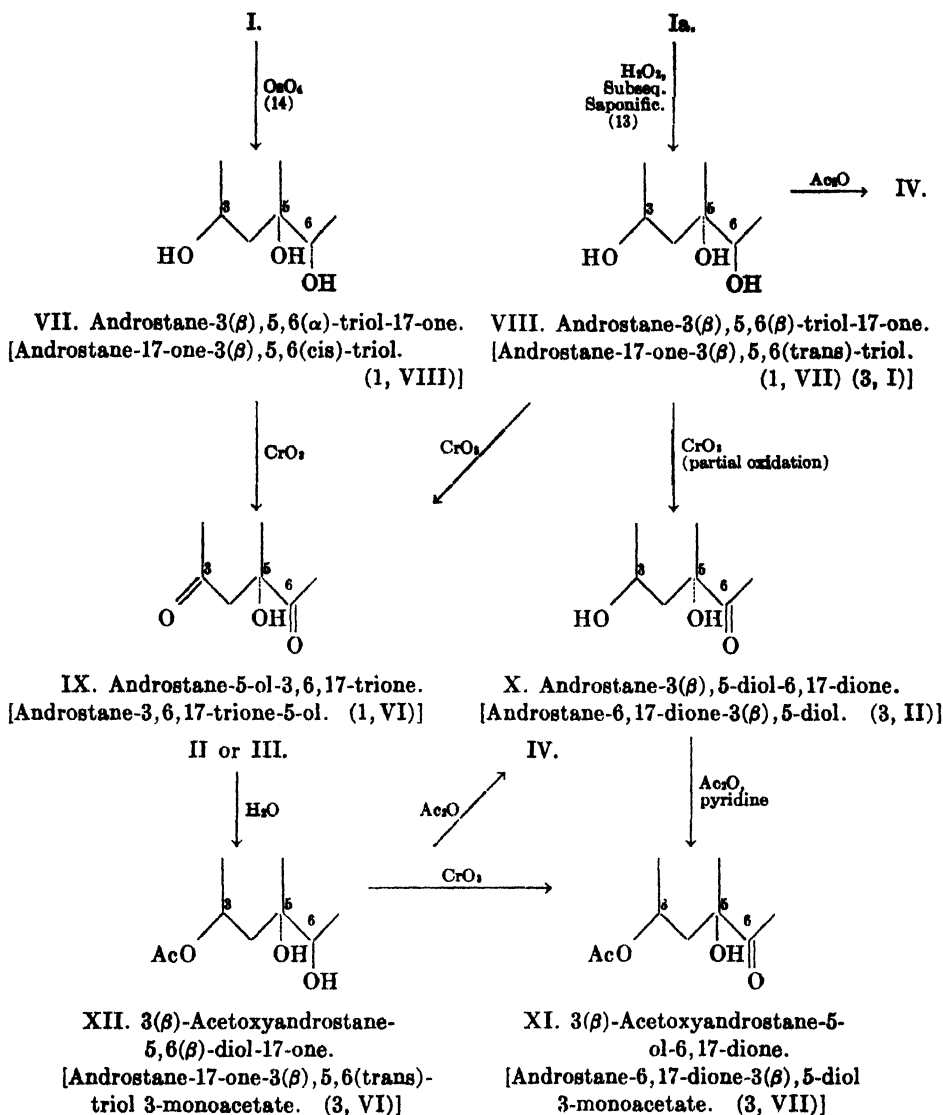
- V. 3(β),5-Diacetoxyandrostane-6(β)-ol-17-one.
 [Androstane-17-one-3(β),5,6(trans)-triol 3,5-diacetate. (4, XI)]

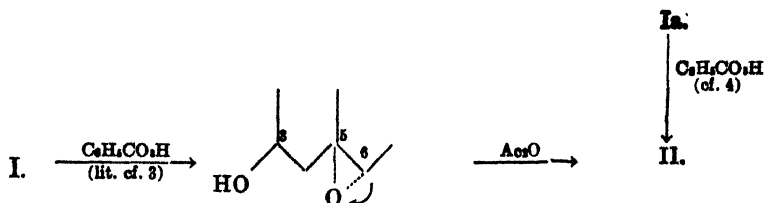
Ac₂O + HCl gas

Ac₂O



- VI. 3(β),5,6(β)-Triacetoxyandrostane-17-one.
 [Androstane-17-one-3(β),5,6(trans)-triol triacetate. (4, XII)]



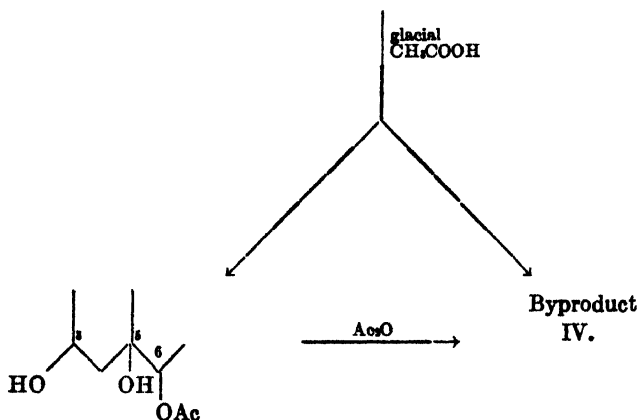


XIII. 5,6(α)-Oxidoandrostane-3(β)-ol-17-one.

[Dehydroisoandrosterone oxide,

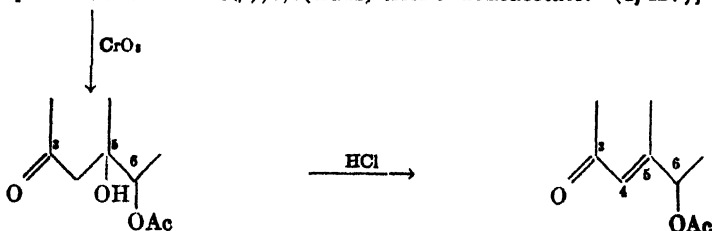
Androstane-(5,6)(β)-oxide-17-one-3(β)-ol. (3, IX)]

[Androstane-(5,6)(α)-oxide-17-one-3(β)-ol. (4, XIV)]



XIV. 6(β)-Acetoxyandrostane-3(β), 5-diol-17-one.

[Androstane-17-one-3(β), 5,6(trans)-triol 6-monoacetate. (4, XV)]



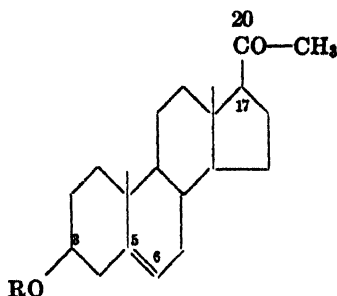
XV. 6(β)-Acetoxyandrostane-5-ol-3,17-dione.

[Androstane-3,17-dione-5,6(trans)-diol 6-monoacetate. (4, XVI)]

XVI. 6(β)-Acetoxy- Δ^4 -androstene-3,17-dione.

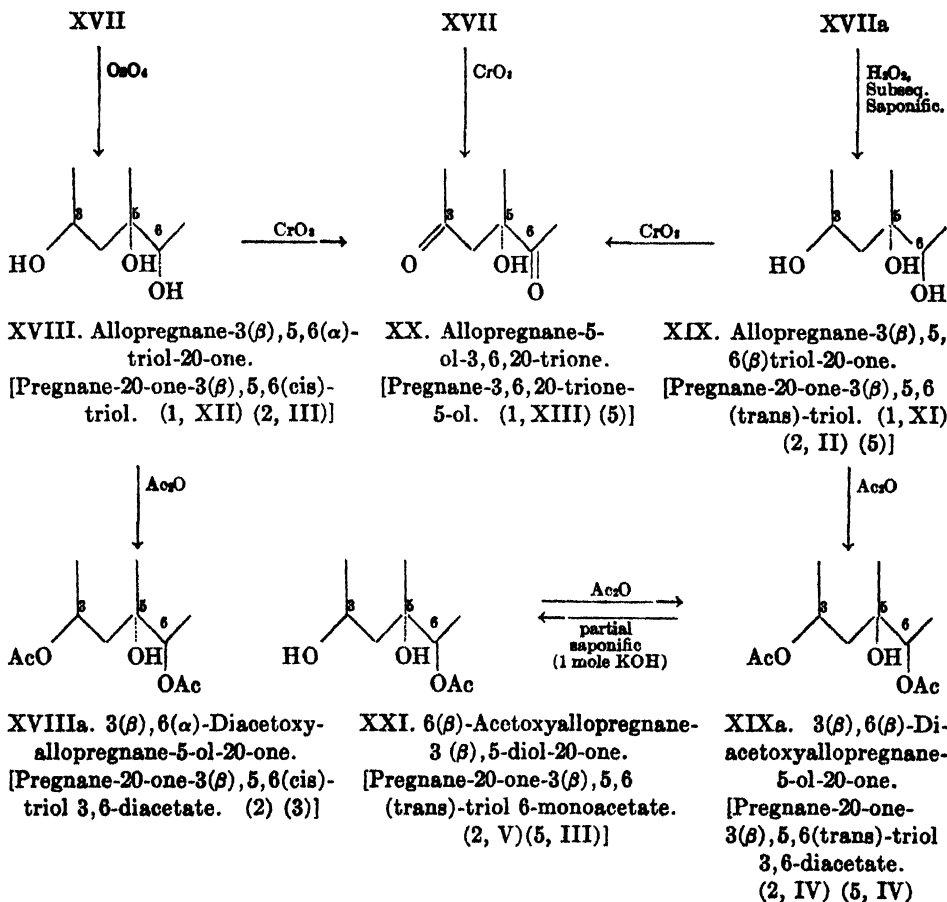
[4-Androstene-3,17-dione-6(α)-ol acetate; 6(α)-acetoxy-4-androstene-3,17-dione. (4, XVII)]

The second series of reactions are derived from pregnenolone (XVII):



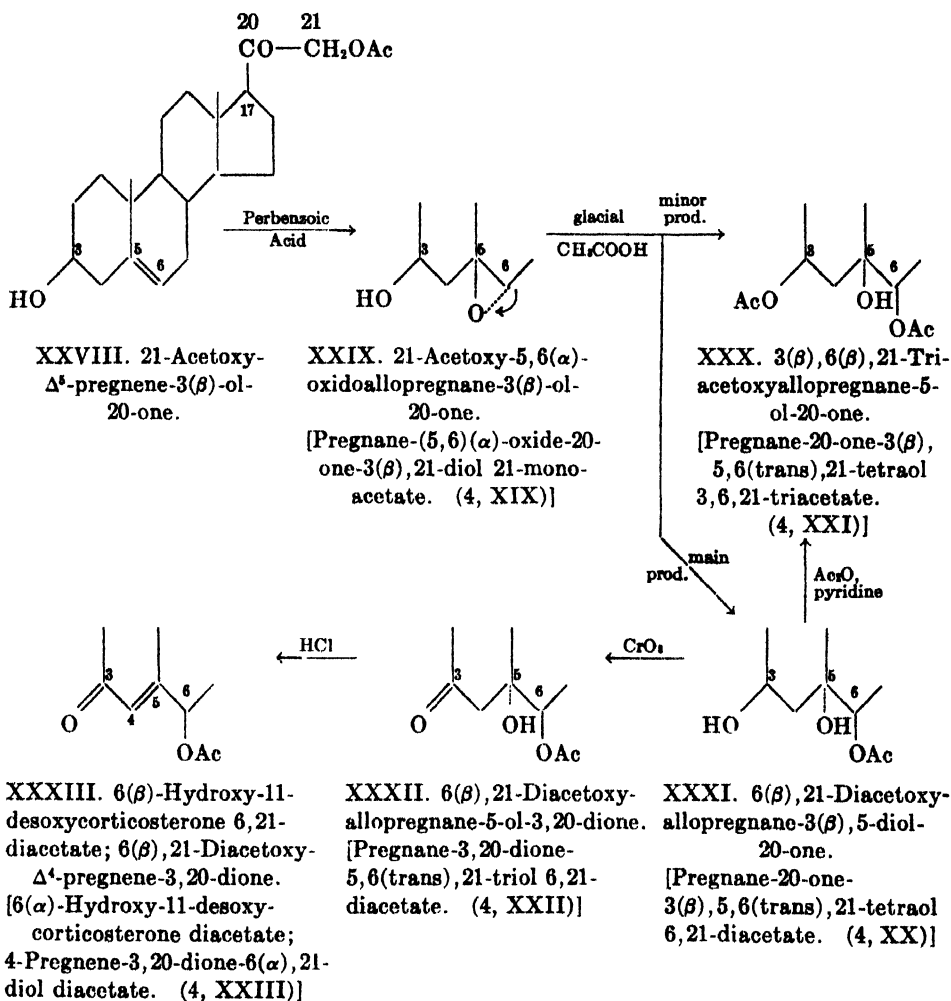
XVII. R = H, Δ^5 -Pregnene-3(β)-ol-20-one.

XVIIa. R = Ac, 3(β)-Acetoxy- Δ^5 -pregnene-20-one.



As was stated in a previous communication (2), the alkaline hydrolysis of 6(β)-acetoxyprogesterone (XXIV) does not yield the 6(β)-hydroxyprogesterone (XXV) which is obviously unstable and rearranges to a compound which is identical with the allopregnane-3,6,20-trione (XXVI) obtained from hyodesoxycholic acid in the laboratory of Hoehn (15). These authors observed that pregnane-3,6,20-trione undergoes rearrangement to allopregnane-3,6,20-trione under the influence of mineral acid or alkali.

A third series of reactions are derived from 21-acetoxypregnenolone (XXVIII):



With the above changes of nomenclature complete analogy exists regarding the behavior of the 5,6-oxides and 3,5,6-triols derived from cholesterol (6, 16) and those derived from dehydroisoandrosterone (I), pregnenolone (XVII) and 21-acetoxypregnenolone (XXVIII) respectively.⁴

⁴ No definite configurations can as yet be assigned to some compounds obtained from a 5,6-oxide of Δ^4 -pregnene-3(β),20,21-triol by means of a Grignard reaction (17).

Addition: Lardon (18) in Reichstein's laboratory recently studied the partial saponification of methyl 3(α), 7(α), 12(α)-triacetoxyetiocholanate. He presented convincing evidence that the monoacetoxy compound present in the resulting mixture of reaction products is methyl 3(α), 12(α)-dihydroxy-7(α)-acetoxyetiocholanate. In a paper dealing with some degradation products of cholic acid (19) we described the partial saponification of 3(α), 7(α), 12(α)-triacetoxypregnane-20-one which yielded a monoacetoxy compound interpreted to be 12(α)-acetoxypregnane-3(α), 7(α)-diol-20-one. The identical substance was subsequently described by others (20). On account of his findings in connection with the partial hydrolysis of methyl 3(α), 7(α), 12(α)-triacetoxyetiocholanate Lardon (18) presumes that the 12-acetoxypregnane-3(α), 7(α)-diol-20-one described by us (19) and Miescher (20) is in reality 7(α)-acetoxypregnane-3(α), 12(α)-diol-20-one. This assumption is probably correct and hence the product of the oxidation of the latter compound with chromic acid (19) should be called 7(α)-acetoxypregnane-3,12,20-trione rather than 12(α)-acetoxypregnane-3,7,20-trione. In like manner the product of the partial dehydrogenation of the compound by means of the Oppenauer method (19) should be named 7(α)-acetoxypregnane-12(α)-ol-3,20-dione rather than 12(α)-acetoxypregnane-7(α)-ol-3,20-dione.

The author is indebted to Dr. William H. Pearlman for his valuable suggestions.

SUMMARY

The naming of a number of compounds described in previous publications (1, 2, 3, 4, 5, 19) has been revised to conform with the latest nomenclature.

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VINYL ETHERS OF ALKYL HYDROXYACETATES AND THEIR POLYMERS

D. D. COFFMAN, G. H. KALB, AND A. B. NESS

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A variety of products result from the reaction of acetylene with hydroxyl-containing organic compounds, depending upon the reactants and conditions. In the presence of alkaline catalysts, acetylene reacts with monohydric alcohols to form vinyl ethers (1), while with neutral mercuric salts or acidic catalysts, acetals are formed, presumably through the intermediate vinyl ether (2). In extending this reaction to hydroxycarboxylic acids, Nieuwland obtained cyclic acetals from lactic acid and higher homologs, while hydroxyacetic acid did not react (3).

It has been found that in the presence of acidic catalysts, alkyl hydroxyacetates react with acetylene, giving good yields of acetaldehyde di(carbalkoxymethyl) acetals. The acetals can be pyrolyzed to the corresponding vinyl ethers.

The acetaldehyde di(carbalkoxymethyl) acetals were prepared readily from methyl hydroxyacetate and isobutyl hydroxyacetate in 70–80% yields, by passing acetylene at atmospheric pressure over the ester containing mercuric oxide and a boron trifluoride/methanol complex (4) as catalyst. This method is superior in simplicity and performance to the use of mercuric phosphate catalyst and acetylene under pressure, which gives about 56% yields.

The vinyl ether was obtained conveniently by pyrolysis of the acetal at 300° over a silver-on-asbestos catalyst. In this way, carbomethoxymethyl vinyl ether was obtained in 70–82% yields, based on the acetal consumed (5). The conversions ranged from 45–70% per pass.

Carbomethoxymethyl vinyl ether polymerized rapidly and nearly quantitatively at –78° with boron trifluoride catalyst in methylene chloride solution, forming plastic, rubber-like polymers which resembled polyisobutylene and were soluble in the common halogenated and oxygenated organic solvents (6). The polymers underwent reactions typical of the carbomethoxy group. Hydrolysis gave water-soluble polycarboxylic acids. Reaction with ammonia gave low-melting, water-soluble amides, insolubilized by treatment with formaldehyde.

Carbomethoxymethyl vinyl ether copolymerized with isobutylene using boron trifluoride catalyst in methylene dichloride, yielding rubber-like products. Copolymers containing 5–9% of combined ether were soluble plastics somewhat more rubbery than the polyisobutylene control. Copolymerization of carbomethoxymethyl vinyl ether with propylene and with isobutyl vinyl ether gave viscous polymers containing 20–25% of combined carbomethoxymethyl vinyl ether.

EXPERIMENTAL

Acetaldehyde di(carbomethoxymethyl)acetal. A mixture of 15 g. of boron trifluoride/methanol (1:1 mole ratio) complex and 3 g. of mercuric oxide was introduced into a

1-liter, 3-necked flask, equipped with stirrer, thermometer, and an acetylene inlet tube. The mixture was heated until about one-half the mercuric oxide had dissolved. After cooling, 540 g. (6 moles) of methyl hydroxyacetate was added. The flask was cooled externally to maintain the temperature at 25–30°. Acetylene, purified by scrubbing with water, by passing over sodium hydroxide pellets, and by drying over calcium chloride and phosphorus pentoxide, was passed at atmospheric pressure over the surface of the vigorously stirred mixture. The acetylene was absorbed very rapidly (about 1 liter/min.), and the reaction was exothermic. The introduction of acetylene was stopped after 68 g. (2.6 moles) of acetylene had been absorbed.

The water cooling-bath was replaced with an ice-bath, and 20 g. of solid sodium carbonate was added to the well-stirred mixture. After 10 minutes, 50 cc. of saturated sodium carbonate solution was added. The dark-colored reaction mixture became light yellow in color. After 10 minutes, an equal volume (500 cc.) of ether was added. The aqueous phase was separated, and the ethereal solution was dried over anhydrous potassium carbonate. After filtration, the ether was evaporated, and the residue was distilled from a 1-liter modified Claisen flask equipped with a 15-inch column. A fraction of 308 g. (81% yield based on the acetylene absorbed) distilling at 115–120°/2–3 mm. was collected as acetaldehyde di(carbomethoxymethyl) acetal. A sample fractionated through a 15-inch Fenske column had the following properties: b.p. 114–116°/2 mm.; n_D^{25} 1.4308; d_4^{25} 1.1652.

Anal. Calc'd for $C_8H_{14}O_6$: C, 46.60; H, 6.85; M_R , 45.74.

Found: C, 46.72; H, 7.12; M_R , 45.72.

Acetaldehyde di(carbomethoxymethyl) acetal was also obtained by reacting methyl hydroxyacetate with acetylene under 250 lb./sq.in. pressure at 70° using 10% mercuric phosphate catalyst (Eimer and Amend). During reaction the temperature in the bomb increased to 95°. After acetylene adsorption had ceased (1.5 hours), the reaction product was removed, the mercuric phosphate was filtered from the liquid portion, and the filtrate was dried over anhydrous potassium carbonate. Distillation at reduced pressure gave a 56% yield of acetal which had physical properties in agreement with those listed previously.

Acetaldehyde di(carbisobutoxymethyl) acetal. Two grams of mercuric oxide was dissolved in 10 g. of boron trifluoride/methanol complex. To this was added 528 g. (4 moles) of isobutyl hydroxyacetate. The reaction was carried out in the same manner as in the case of the methyl ester and was stopped when the theoretical amount of acetylene (52 g. or 2 moles) had been absorbed. The reaction mixture was worked up in a similar manner. On fractionation a 400-g. sample of acetaldehyde di(carbisobutoxymethyl) acetal, distilling at 128–134°/2–3 mm., was collected. The yield was 70%. Refractionation through a 15-inch Fenske column gave a sample which had the following properties: b.p. 130–131°/2 mm.; n_D^{25} 1.4308; d_4^{25} 1.0204.

Anal. Calc'd for $C_{14}H_{26}O_6$: C, 57.86; H, 8.97; M_R , 73.32.

Found: C, 57.73; H, 9.10; M_R , 73.5.

Pyrolysis of acetaldehyde di(carbomethoxymethyl) acetal. Acetaldehyde di(carbomethoxymethyl) acetal (748 g.) was pyrolyzed over an asbestos-supported silver catalyst (7) at 260–300° at the rate of 1.45 g./min. Distillation of the condensate through a 24-inch Fenske column gave a fraction (482 g.) boiling at 71.5–73.5°/47–49 mm. along with 235 g. of recovered acetal. The 482 g. fraction, consisting of a mixture of methyl hydroxyacetate and the vinyl ether, was washed with an equal volume of water. Before separating the layers, a volume of diethyl ether equal to the volume of the aqueous layer was added. After extraction, the aqueous layer was separated and again extracted with a small amount of diethyl ether. The combined ethereal solution was repeatedly washed with equal volumes of water and was then dried over anhydrous potassium carbonate and sodium sulfate. After filtering off the solid material and evaporation of the diethyl ether, the residue was fractionated. A 222-g. fraction (yield 82% based on acetal consumed) distilling at 76.7°/49.5 mm. was obtained as the vinyl ether of methyl hydroxyacetate. Carbomethoxymethyl vinyl ether prepared in this way had the following properties: b.p. 76.7°/49.5 mm.; n_D^{25} 1.4232; d_4^{25} 1.0531.

Anal. Calc'd for $C_5H_8O_3$: C, 51.72; H, 6.90; sap. no., 116; M_n , 28.11.

Found: C, 51.96; H, 7.13; sap. no. 116.8; M_n , 28.06.

Polymerization of carbomethoxymethyl vinyl ether. A solution of 10 g. of vinyl ether in 70 g. of methylene chloride, contained in a reaction tube fitted with a sealed stirrer and gas inlet and outlet vents, was cooled in a bath at -78° . After the air had been displaced with dry nitrogen, 0.1 g. of anhydrous boron trifluoride gas was introduced over the well-stirred solution. Vigorous polymerization occurred almost immediately as evidenced by the evolution of heat. After 2 hours at -78° , the catalyst was destroyed by the addition of 2 g. of anhydrous ammonia. The reaction mixture was warmed to room temperature, and the colorless viscous solution was filtered to remove inorganic salts. After concentration of the polymer solution by distilling off about one-half the methylene chloride, the polymer was thrown out of solution by dilution with diethyl ether. The carbomethoxymethyl vinyl ether polymer (10 g.) so obtained was plastic and rubbery. It had an intrinsic viscosity of 4.9 (determined at 25° in chloroform at a concentration of 1 g./1000 cc. of solution) as calculated from the equation $N_i = \frac{(N_r - 1)}{C}$, in which N_i is intrinsic viscosity, N_r is relative viscosity, and C is moles of solute per liter of solution.

The carbomethoxy group in the polymer undergoes normal transformations. Hydrolysis occurred when a methanol/benzene solution of the polymer was refluxed with excess potassium hydroxide. The hydrolysis product was isolated by the addition of acetone to the concentrated, acidified aqueous solution. The polycarboxylic acid obtained corresponded to a conversion of 59% of the carbomethoxyl groups to carboxyl groups. The light brown acid was soluble in water, insoluble in common organic solvents, and became tacky when heated on a copper block at 150° .

Treatment of the polymer in benzene/ethanol solution with liquid ammonia gave a product corresponding to the conversion of 70% of the carbomethoxyl groups to amide groups. The dark colored product was soft and tacky. It was soluble in water and insoluble in acetone and benzene. It was insolubilized by reaction with aqueous formaldehyde in the presence of alkali followed by heating at 100° .

Copolymerization of carbomethoxymethyl vinyl ether and isobutylene. A solution of 1 g. of the carbomethoxymethyl vinyl ether, 35 g. of trichloroethylene, 11 g. of isobutylene, and 33 g. of propane was placed in the polymerization vessel and cooled to -78° . To the stirred solution was added 0.9 g. of anhydrous boron trifluoride in 0.3-g. portions. Very vigorous polymerization ensued, giving a viscous solution. After 3 hours, 5 g. of anhydrous ammonia was added to destroy the catalyst. The cooling bath was removed, and the solution was warmed to room temperature. Dilution of the solution with diethyl ether gave 12 g. of a colorless, plastic, rubbery copolymer of intrinsic viscosity 4.4 as determined on a 0.1% solution in tetralin. The copolymer carbon content of 83.46% and hydrogen content of 13.90% indicated a composition corresponding to a 94:6 weight ratio of isobutylene to carbomethoxymethyl vinyl ether.

Copolymerization of carbomethoxymethyl vinyl ether and propylene. A solution of 2.5 g. of vinyl ether, 25 g. of propylene, and 35 g. of methylene chloride, contained in a polymerization vessel under an atmosphere of dry nitrogen, was cooled to -78° . Above the well-stirred solution was introduced 3 g. of anhydrous boron trifluoride. After 72 hours at -78° , 5 g. of anhydrous ammonia was added to destroy the catalyst, and the mixture was warmed to room temperature. The solvent was removed from the filtered solution by evaporation at reduced pressure. The tan-colored, viscous polymer (13 g.) obtained had a saponification equivalent of 504, indicating a propylene/carbomethoxymethyl vinyl ether weight ratio of 79/21.

Copolymerization of carbomethoxymethyl vinyl ether and isobutyl vinyl ether. A solution of 1 g. of carbomethoxymethyl vinyl ether and 15 g. of isobutyl vinyl ether in 70 g. of methylene chloride, contained in a polymerization vessel under an atmosphere of dry nitrogen, was cooled to -78° . Polymerization was induced by adding 0.3 g. of anhydrous boron trifluoride. After an induction period of about 10 minutes, rapid polymerization occurred.

After 16 hours at -78° , the catalyst was destroyed by the addition of 2 g. of ammonia. The solution was warmed to room temperature, and the solvent was removed from the filtered solution by evaporation at reduced pressure. There was obtained 10 g. of a viscous copolymer having a saponification equivalent of 456, indicating an isobutyl vinyl ether/carbomethoxymethyl vinyl ether weight ratio of 75/25. The copolymer was soluble in ether, acetone, ethyl acetate, ethyl alcohol, and toluene but was insoluble in aliphatic hydrocarbons and water.

SUMMARY

A convenient method for the preparation of the acetals of methyl hydroxyacetate and isobutyl hydroxyacetate has been described. Pyrolysis of acetaldehyde di(carbomethoxymethyl) acetal gives the polymerizable vinyl ether of methyl hydroxyacetate.

WILMINGTON, DELAWARE

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BRANCHED-CHAIN FATTY ACIDS. VI. RELATIONSHIP OF MELTING POINT TO STRUCTURE. NEW METHOD OF SYNTHESIS OF ACIDS CONTAINING A QUATERNARY CARBON ATOM

JAMES CASON

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Since the higher fatty acids often form mixed crystals showing a relatively sharp melting point which is not changed by recrystallization, it is often troublesome to determine whether an acid melting lower than the normal isomer is a branched-chain acid or a fortuitous mixture giving the observed molecular weight. Although the accumulation of data concerning the properties of pure synthetic branched-chain acids is not yet great, it seems possible that certain useful predictions may soon be made concerning the melting points possible for a branched-chain acid of a given molecular weight.

A full consideration of the relationship of melting point to the position of a branching methyl group is best deferred until additional syntheses of methyl-octadecanoic and methyltetracosanoic acids in progress in this laboratory are completed and reported. It has already been shown by Weitkamp (1), however, that the iso acid (branching group on the carbon next to the end of the chain) always melts one degree or less below the normal isomer, for acids with fourteen or more carbons, while the *d*-anteiso acid (branching group on the third carbon from the end of the chain) always melts considerably lower than this, 14–24° below the normal isomer. Schneider and Spielman (2) have prepared a series of 2-methyl acids, and all of them melted 11–14° below the normal isomers. A consideration of the melting points of the synthetic 3- (3), 10- (4, 5), 15- (6), and 16-methyloctadecanoic (7) acids, as well as 6- (7), 10- (2, 7), and 14-methyltetracosanoic (6) acids makes it apparent that the 2-methyl acid and anteiso acid have melting points higher than any acid of the same molecular weight with the branching methyl group attached to a carbon between these two positions.

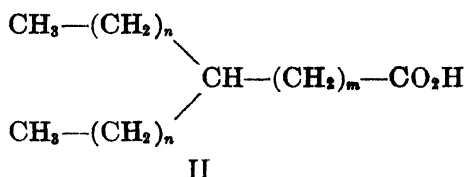
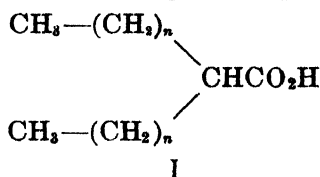
In the instances of 10-methyloctadecanoic acid, 16-methyloctadecanoic acid and 2-methylhexacosanoic acid (2, 8), both *dl*- and optically active isomers have been obtained, and in each case the optically active forms melted below the *dl*-isomer. The *dl*-16-methyloctadecanoic acid (C_{18} anteiso acid) (7) melted about 4° above the *d*-isomer (1). Thus, it seems safe to say that no methyl substituted acid, except the iso acid, can have a melting point less than 10° below that of the normal isomer, and the iso acid melts no more than 1° below the normal isomer. The only additional data which seem desirable in support of this statement are the melting points of *dl*-anteiso acids with twenty-four or more carbons.

These conclusions are based on consideration of acids containing an odd number of total carbon atoms, thus an even number of atoms in the straight-chain portion of the acid. In such instances, the lowering of the melting point caused by introduction of the branching methyl group is nearly the same when referred to the normal acid corresponding to the straight-chain portion of the molecule, or to the normal acid corresponding to the total number of carbons in the branched-chain acid. This follows from the fact that an odd-carbon normal acid

having $n+1$ carbon atoms has nearly the same melting point as the even-carbon acid containing n carbon atoms. Actually, in the case of 15-methylheptadecanoic acid (9), the point of reference appears to be the normal acid corresponding to the straight-chain portion of the molecule. This acid melts at $43.5\text{--}43.7^\circ$, 17.6° below the melting point of n -heptadecanoic acid, a differential corresponding well with the 19° -differential between 16-methyloctadecanoic acid and n -octadecanoic acid (stearic acid). If the 15-methylheptadecanoic acid is related to stearic acid, there is no such correspondence. Thus, so far as may be deduced from this single known example, it appears that a methyl-substituted branched-chain acid (other than the iso acid) with an even number of carbon atoms must melt even more than 10° below the normal isomer.

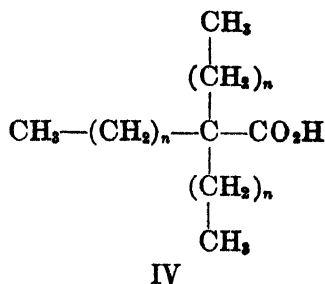
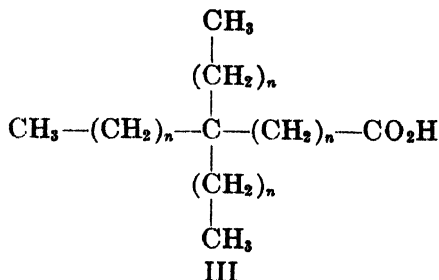
Thus, there is a region of at least ten degrees just below the melting point of the normal isomer where a methyl-substituted acid cannot melt, and it seems certain that introduction of additional methyl groups or replacement of methyl by a larger group would not ordinarily give a melting point in this "excluded region". Since several C_{24} acids (10) and one C_{26} acid (11) have been reported as melting in this "excluded region", it becomes of interest to consider whether any special structures might permit a branched-chain acid to melt in this region.

The very high melting point of the iso acids is striking and difficult to explain unless it be attributed to the symmetrical end-grouping. Thus, other types with similar structures, such as represented by formulas I and II, might also have relatively high melting points.



Data in the literature exclude the possibility of type I having such a melting point. Dioctylacetic acid (12) melts at $35\text{--}36^\circ$, didodecylacetic acid (13) melts at $70\text{--}71^\circ$, and dihexadecylacetic acid (14) melts at $68\text{--}69^\circ$. Although there is no information in the literature concerning acids of type II, work in progress in this laboratory has shown that acids of this type, where n is 1 or 2 and m is much larger, have relatively low melting points. Thus, the high melting points of the iso acids remain without analogy.

Other structures which might result in high melting points are the symmetrical types represented by formulas III and IV. Trimethylacetic acid (15) melts at about 35° , while triethylacetic acid (16) melts at about 39° .



These data suggest that higher molecular weight acids of these types might have relatively high melting points. However, no acids of this type have been synthesized, and the synthesis of such types proves very difficult. Robinson and co-workers (17), also Buu-Hoï and Cagniant (18), have made a study of the synthesis of acids containing a quaternary carbon, and it was found that the introduction of two large groups on the quaternary carbon is very difficult. The introduction of three groups, all larger than ethyl, was not attempted. All syntheses developed for introduction of two large groups on the quaternary carbon were tedious and gave very low over-all yields.

It would seem that the most hopeful approach to this problem is introduction on the quaternary carbon of relatively small groups containing terminal functional groups of such a nature that the chains may be extended as desired *after* the step creating the quaternary carbon. These later reactions would then involve groups somewhat removed from the highly hindered center. Of the various starting compounds which might be considered, the γ -cyano aldehydes and γ -cyano ketones obtained by the cyanoethylation reaction of Bruson and Riener (19) seem promising. The present paper reports the development of a synthesis of acids containing a quaternary carbon, starting with 2-ethyl-2-(β -cyanoethyl)hexanal (V) (19). It is hoped that the method may be extended to synthesis of compounds of types III and IV.

The cyano aldehyde, V, readily obtained in quantity and in the yield previously reported (19), was converted in high yield to α -butyl- α -ethylglutaric acid (VI), which was also obtained by Bruson and Riener. On account of the great hindrance around one carboxyl in this acid, it may be converted in excellent yield to either of the two possible half esters. The unhindered carboxyl is esterified by heating for one hour with a large excess of methanol, in the presence of an acid catalyst. Under these conditions no more than a trace of di-ester or di-acid is recovered. Even when the heating period is extended to one hundred forty hours a 10% yield of half ester is obtained; so the essential homogeneity of the half ester, VIII, seems assured. The same half ester is obtained when the acid is first converted to the anhydride, VII, and this allowed to react with methanol. The other half ester, X, is obtained by saponification of the di-ester, IX, with 1.1 equivalent of alkali. Essentially no di-acid is obtained, even when the amount of alkali is increased to 1.25 equivalent.

It was initially assumed that if the half ester, X, were converted to its acid chloride and this allowed to react with dibutylcadmium, the keto ester, XII, would be obtained. This procedure gave a keto ester of the expected composition, and when this keto ester was reduced by the modified Wolff-Kishner procedure (20), there was obtained a liquid acid of the composition and molecular weight expected for *n*-butylethyl-*n*-heptylacetic acid (XIV). When this acid was converted to solid derivatives it became apparent that something was amiss, for the derivatives melted over ranges of ten to fifty degrees, and no sharp-melting products could be obtained by repeated fractional crystallization. As has been briefly reported (21), this behavior has been traced to the fact that the ester acid chloride of either of the half esters, VIII and X, rearranges to a

mixture of the two possible ester acid chlorides. Thus, the same tribromoanilide is obtained from either of the half esters. The structure, XI, is assigned to this tribromoanilide, since formation of the other isomer would be subject to high hindrance.

As has been mentioned (21), such a rearrangement of ester acid chlorides has been observed previously, but the mixture of products obtained was ascribed to the starting half esters being non-homogeneous. There are several examples (22), in the literature where ester acid chlorides of unsymmetrical succinic or glutaric acids have been used in synthesis; however, the data are not sufficient to show whether there was rearrangement. There is one instance (23), however, where the data show clearly that such an ester acid chloride was used without rearrangement. In this case, two carbons of the glutaric acid were part of a six-membered ring, and this may have hindered rearrangement; however,

TABLE I
EFFECT OF TEMPERATURE ON REARRANGEMENT

REACTION		COMPOSITION OF PRODUCT	
VIII	via distilled acid chloride →	XII	61%
		XIII	39%
VIII	via acid chloride below 40° →	XII	42%
		XIII	58%
X	via distilled acid chloride →	XII	55%
		XIII	45%
X	via acid chloride below 40° →	XII	68%
		XIII	32%

it is also true that this ester acid chloride was handled rapidly at temperatures below 40°. When our ester acid chlorides were prepared and used in the cadmium reaction at temperatures of 40° or less, again rearrangement occurred, but less than when the acid chlorides were heated. The composition of the keto ester was determined by separation of the two keto esters or of the acids obtained after Wolff-Kishner reduction. It seems worthy of comment that the excellent procedure of Huang-Minlon (20) gave a 41% yield on reduction of the hindered carbonyl in XIII. The reduction of such hindered carbonyl groups by other methods (*cf.* ref. 17) has been tried, but without success. The data summarized in Table I show that rearrangement occurs, in part at least, after the acid chloride is formed.

A similar rearrangement has been reported by Prelog and Heimbach-Juhász (24), who observed that γ -ethoxybutyryl chloride rearranges nearly quantita-

tively into ethyl γ -chlorobutyrate when heated at 100°. Since such a rearrangement did not occur with ϵ -ethoxycaproyl chloride, it was postulated and supported by rate measurements that the rearrangement is intramolecular and a cyclic oxonium salt is the intermediate in the rearrangement. A similar explanation has been presented by Johnson and Goldman (25) to explain the ester exchange observed when certain itaconic acid half esters were heated with zinc chloride in acetic acid. Such a hypothesis seems the most reasonable explanation of the rearrangement of ester acid chlorides, and if this is the case only derivatives of succinic and glutaric acids should show this behavior. Although this rearrangement lowers the yield of either quaternary carbon acid eventually obtained, it does not defeat the synthesis, for the two products may be separated essentially quantitatively. When a mixture of the acids, XIV and XV, is heated for two hours with a large excess of methanol in the presence of sulfuric acid, the unhindered isomer (XV) is esterified quantitatively while the hindered isomer (XIV) is essentially unattacked. The keto acids behave similarly. Controlled saponification is only slightly less selective, and the combination of the two processes or repetition of one process gives products of high purity.

Since treatment of the anhydride, VII, with methanol gave only the half ester, VIII, it was hoped that reaction of this anhydride with dibutylcadmium would give only one keto acid, XVI, resulting from addition of butyl at the unhindered carbonyl. Surprisingly enough, the keto acid obtained from this reaction consisted of only 31.5% of this isomer (XVI), the remaining 68.5% being the isomer (XVII) resulting from addition of butyl to the hindered carbonyl. This seems conclusive proof that organocadmium reagents do not react with acid anhydrides and, by inference, acid chlorides by addition to the carbonyl group, for such a mechanism could hardly permit the observed distribution of isomers just mentioned. If, on the other hand, the initial stage of the reaction is approach of cadmium to the central oxygen of the anhydride, followed by breaking of the linkage from oxygen to one or the other of the carbonyl carbons, then the above distribution of isomers is reasonable, for the $-CdO-$ grouping would prefer the unhindered carbonyl. Once this structure is established, the butyl group has no choice but to become attached to the hindered carbonyl. This mode of reaction is consistent with evidence (26) that the mechanism of the reaction of a Grignard reagent with acid halides is different from that of the organo compounds of mercury, zinc, and cadmium.

It seems possible that a different sequence of manipulation of the groups in a cyano aldehyde such as V could result in a synthesis of quaternary-carbon acids not beset by the difficulties encountered in the present work. This is being further investigated.

EXPERIMENTAL

Microanalyses are by C. W. Koch and V. H. Tashinian. All melting points are corrected, all boiling points uncorrected. All distillations, unless otherwise specified, were through a half-meter column of Vigreux type or Podbielniak type. Pressure was measured with a Zimmerli gage and subject to a probable error of 0.2-0.3 mm. of mercury.

α -Butyl- α -ethylglutaric acid (VI) (19). The cyano aldehyde (V) was prepared as described previously (19), the yields being 79–83.5% in runs varying from 0.1 mole to 3.6 moles, b.p. 119–120° (2 mm.), n_D^{20} 1.4508. Hydrolysis of V to γ -ethyl- γ -formylcaprylic acid was accomplished with aqueous alkali as described by Bruson and Riener except that extension of the heating period to seven hours raised the yield to 87.5% in a 2.75 mole run; b.p. 140–141° (1.25 mm.), n_D^{20} 1.4550. Hydrolysis with various concentrations and equivalencies of alcoholic alkali gave a much lower yield, as did hydrolysis with sulfuric acid in aqueous acetic acid. These latter methods also gave poor material balances, presumably on account of partial reversal of the cyanoethylation reaction.

After trial of several procedures, the permanganate oxidation to VI was modified as follows. In a solution of 160 g. of potassium hydroxide in 2.4 liters of water was dissolved 400 g. (2 moles) of aldehyde acid. To the stirred mixture was added during one hour 316 g. (2 moles) of solid potassium permanganate, the temperature being maintained at 45–50° by external cooling. After stirring for an additional hour at this temperature, the manganese dioxide was removed and extracted on the steam-bath with 500-cc. and 250-cc. portions of water. The total colorless filtrate was acidified with 450 cc. of concentrated hydrochloric acid. The viscous oil which separated began to crystallize slowly after about three hours, and after about five hours the hard, white crystalline mass was ground and dried in a vacuum. Yield of crude product, 397 g. (91.8%), m.p. 72–78°. This crude acid contains appreciable impurities, but purification by crystallization involves much loss, and purification by distillation at later stages in the synthesis is best. Recrystallization was satisfactory only from nitromethane, from which small, hard crystals separated over a period of two to three days. From 7.9 g. of crude acid was obtained 4.3 g. of pure VI, m.p. 78–80°, not raised by further crystallization; eq. wt. 108 (calc'd 108.1); literature (19) m.p. 81–82°.

α -Butyl- α -ethylglutaric anhydride (VII) was prepared by heating under reflux for one and one-quarter hours a mixture of 50 g. of crude VI and 44 cc. of acetic anhydride. Distillation at 5.5 mm. pressure gave 3.1 g. of fore-run, boiling largely at about 120°, and 33.8 g. (74%) of anhydride, b.p. 153–153.5°. There was a residue of 4.5 g. A center cut, b.p. 153.5°, n_D^{20} 1.4647, was used for analysis.

Anal. Calc'd for $C_{11}H_{18}O_3$: C, 66.65; H, 9.15.

Found: C, 67.00, H, 9.23.

α -Butyl- α -ethyl- γ -carbomethoxybutyric acid (VIII). (A) A mixture of 21.6 g. (0.1 mole) of crude VI, 61 cc. (1.5 mole) of methanol, and 3.8 cc. of concentrated sulfuric acid was heated under reflux for one hour, then poured into 250 cc. of water. The products, obtained after distillation of the material obtained by three extractions with ether, consisted of 2.1 g. of fore-run boiling largely below 110° (3 mm.) and 19.3 g. (84%) of half ester, VIII, b.p. 155–159° (3 mm.). There was only a trace of residue. The fore-run obtained here and in other preparations starting with crude VI is not obtained when pure dibasic acid is used (cf., IX, below). A center cut was used for analysis, b.p., 159° (3 mm.), n_D^{20} 1.4530.

Anal. Calc'd for $C_{12}H_{22}O_4$: C, 62.57, H, 9.63.

Found: C, 62.30, H, 9.53.

(B) A mixture of 12.2 g. of anhydride (VII) and 3.0 cc. of methanol was heated under reflux on a steam-bath for two hours, then distilled at 1 mm. pressure to yield, after only 0.1 g. of fore-run, 13.4 g. (94.3%) of half ester, VIII, b.p. 142.0–142.5°, n_D^{20} 1.4526. The homogeneity of this product was tested by heating it under reflux for one hour with 35 cc. (15 equivs.) of methanol and 2.2 cc. of concentrated sulfuric acid. The product, obtained as in procedure (A), was distilled at 1.5 mm. pressure to give (a) 0.6 g., b.p. 104.2–104.5°, n_D^{20} 1.4417; (b) 0.6 g., b.p. 104.5–147.5°; (c) 11.7 g., b.p. 147.5–148.5°, n_D^{20} 1.4525. There was no residue. The high recovery of half ester with no change in index of refraction, and the very small conversion to di-ester (Frac. a) show that treatment of the anhydride with methanol gives essentially pure VIII.

Dimethyl α -butyl- α -ethylglutarate (IX). (A) Using 151 g. of crude VI, procedure (A) for VIII was followed except that refluxing was continued for one hundred forty hours. The fractions obtained on distillation were (a) 8.2 g., b.p. 80–122° (4 mm.); (b) 100.5 g. (58.8%)

of di-ester, b.p. 122–124° (4 mm.); (c) 2.5 g., b.p. 100.5–141.5° (1 mm.); and (d) 16.0 g. of half ester, VIII, b.p. 141.5–143.5° (1 mm.). There was only 4.4 g. of residue, and no other material was recovered.

(B) A solution of 8.0 g. of recrystallized VI in 50 cc. of ether was treated at 0° with an excess of diazomethane in ether and allowed to stand four hours at 0°. After excess diazomethane had been destroyed with acetic acid, the mixture was distilled to give 8.5 g. (94.5%) of IX, b.p. 122–124° (4 mm.). There was only 0.1 g. of fore-run and no residue. On a larger run in which crude VI was used there was 2.3 g. of fore-run, b.p. 84–119° (4 mm.), and 31.0 g. of di-ester, b.p. 119–124° (4 mm.). For analysis, there was used a center cut, b.p. 124° (4 mm.), n_D^{25} 1.4418.

Anal. Calc'd for $C_{13}H_{22}O_4$: C, 63.90, H, 9.90.

Found: C, 63.47, H, 9.80.

γ -Carbomethoxy- γ -ethylcaprylic acid (X). A solution of 100.5 g. (0.412 mole) of IX in 225 cc. of methanol was mixed with 50 cc. of 2 *N* aqueous sodium hydroxide and heated under reflux. At intervals of fifteen minutes were added additional 50-cc. portions of 2 *N* aqueous alkali, until at the end of one hour a total of 225.5 cc. (0.453 mole) of alkali had been added. The solution remained homogeneous throughout. After the mixture had been heated under reflux for an additional two hours it was diluted with 700 cc. of water, acidified with 50 cc. of concentrated hydrochloric acid, and extracted with three portions of ether. Distillation at 1 mm. pressure of the product obtained from the ether extracts gave 2.7 g. of fore-run, b.p. 97–140°, and 89.0 g. (94%) of half ester, X, b.p. 140–142°. The residue was about 0.1 g. For analysis there was used a center cut, b.p. 141.5° (1 mm.), n_D^{25} 1.4502.

Anal. Calc'd for $C_{12}H_{22}O_4$: C, 62.57, H, 9.63.

Found: C, 62.73, H, 9.78.

Tribromoanilide XI. A mixture of 1.2 g. of distilled acid chloride prepared from either VIII or X, 1.4 g. of tribromoaniline, and 20 cc. of dry xylene was heated under reflux for four hours. After removal of xylene *in vacuo* and addition of 10 cc. of acetone the mixture was allowed to stand forty-eight hours at room temperature and eight to ten hours at 5°. The crystalline tribromoanilide which had separated weighed 0.4–0.6 g. and melted at 121–124.5°. After two additional crystallizations from acetone there were obtained beautiful fibrous needles: from VIII, m.p. 127.3–128.3°; from X, m.p. 126.5–127.5°, mixed m.p. 127.0–128.0°.

Anal. Calc'd for $C_{13}H_{24}Br_3NO_2$: C, 39.88, H, 4.45.

Found: C, 39.94, H, 4.50.

Ester acid chlorides from VIII and X. A mixture of the half ester and 3.0 mole equivalents of purified thionyl chloride was allowed to stand fifteen to seventeen hours at about 20°, evolution of gas continuing for at least four hours. Use of benzene as solvent and pyridine as catalyst, as described by Bachmann *et al.* (23), appeared to have no effect on the reaction. When the acid chloride was to be used in a low-temperature cadmium reaction, excess thionyl chloride was removed *in vacuo* at a bath temperature of 40° or less, then dry benzene was added and removed *in vacuo*, the residue being used for the cadmium reaction. When the acid chloride was distilled there was obtained a 97% yield of colorless product, b.p. 119–123° (1.25 mm.).

Keto esters XII and XIII. (A) *From distilled ester acid chloride.* A benzene (80 cc.) solution of dibutylcadmium prepared in the usual way (27) from 19.8 g. of pure *n*-butyl bromide was heated to boiling with stirring and treated during two minutes with a solution of 18.0 g. of the above ester acid chloride in 35 cc. of benzene. After heating under reflux for an additional one and one-half hours, the reaction was worked up as previously described (27) for keto esters. Distillation gave, after 0.4 g. of fore-run, 15.7–16.8 g. (80.7–86.3%, based on ester acid chloride) of keto ester, b.p. 128–129° (1.5 mm.). A center cut, b.p. 129°, n_D^{25} 1.4485 gave the correct analysis for the keto ester (see below).

(B) *From unheated ester acid chloride.* The procedure was as above except that three equivalents of butyl bromide were used and the ester acid chloride solution was added to the cadmium solution at 4–5° and the mixture was initially stirred without heating. The

temperature rose to 25–30° after twenty-five to thirty minutes, then heat was applied and stirring continued at 35–40° for three to four hours. The reaction was worked up to yield 90.5–91% (based on half ester) of keto ester, b.p. 127.5–128° (1.25 mm.).

Separation of the keto esters is illustrated by the following procedure applied to 53.2 g. of keto ester prepared by procedure (B) from 50 g. of half ester, X. A solution of the keto ester in 453 cc. of methanol was heated under reflux for four hours with 19.7 cc. of 6 *N* aqueous sodium hydroxide (0.6 equiv. of 0.25 *N* alkali). The homogeneous solution was diluted with 1 liter of water and extracted with one 300-cc. portion and three 100-cc. portions of pentane. The pentane extracts, kept separate, were washed in series twice with a mixture of 75 cc. of water and 25 cc. of methanol. From the pentane extracts was obtained 33.5 g. of unsaponified ester, XII, b.p. 129–130° (1.25 mm.). In order to ensure the homogeneity of XII, the saponification and separation procedure was repeated with 0.3 equiv. of alkali. There was recovered 31.5 g. of keto ester, XII, b.p. 126–127° (1 mm.). A center cut, b.p. 127° (1 mm.), n_D^{20} 1.4460 was used for analysis.

Anal. Calc'd for $C_{16}H_{30}O_2$: C, 71.06, H, 11.18.

Found: C, 71.01, H, 11.09.

To obtain the acid, XVII, from the first saponification the total aqueous extracts were concentrated to about 400 cc., acidified with 15 cc. of concentrated hydrochloric acid, and extracted with three portions of hexane. On concentrating the washed and dried hexane extracts to dryness in a vacuum, there was obtained a residue consisting of 18.0 g. of a slightly yellow viscous oil. From the second saponification there was similarly obtained 1.7 g. of oil. The much smaller amount of keto acid obtained on the second saponification suggests that this acid is largely XVI and that a similar amount of XVI should be present in the first lot of 18.0 g.; this is supported by the results of the esterification described below. An attempt was made to obtain a solid *p*-bromoanilide from 1.0 g. of the second lot (1.7 g.) of keto acid, by reaction of the acid chloride with *p*-bromoaniline, but no crystalline material could be isolated.

The total remaining keto acid (18.7 g.) was heated under reflux for two hours with 75 cc. (25 equivs.) of methanol and 3 cc. of concentrated sulfuric acid. The mixture was diluted with 300 cc. of water and extracted with three portions of pentane. The combined pentane extracts were extracted with a mixture of 75 cc. of water, 25 cc. of methanol and 5 cc. of 6 *N* sodium hydroxide. The work-up for neutral and acidic fractions was continued as described above. Distillation of the neutral fraction gave, after 0.3 g. of fore-run, 16.7 g. of keto ester, XIII, b.p. 133.5–135.5° (1.5 mm.). A center cut, b.p. 135.5° (1.5 mm.), n_D^{20} 1.4500, was used for analysis.

Anal. Calc'd for $C_{16}H_{30}O_2$: C, 71.06, H, 11.18.

Found: C, 70.68; H, 11.05.

From the acidic fraction there was obtained 2.4 g. of a slightly yellow oil, presumably XVI.

The data in this section were used for calculation of the composition of product in the last line of Table I.

n-Butylethyl-*n*-heptylacetic acid (XIV). Although the exact Wolff-Kishner procedure described by Huang-Minlon (20) gave rather low yields with our keto acids, more drastic conditions gave excellent results. The following procedure was standardized by reduction of pure keto esters and the yield data applied to analysis of mixtures of keto esters or acids by separation of the reduced acids.

A mixture of 16.5 g. of pure keto ester, XII, 11.9 g. of potassium hydroxide, 11.3 cc. of 85% hydrazine hydrate, and 85 cc. of diethylene glycol was heated under reflux in a salt-bath for two hours (temperature of refluxing mixture, ca. 135°). The potassium hydroxide does not dissolve until the mixture reaches boiling, then dissolves rapidly with vigorous evolution of heat. Caution is necessary to prevent material from being driven out the top of the condenser; the flask should be less than half full. After the reflux period, the condenser was removed and the temperature of the salt-bath raised to 225–230° during about

fifteen minutes, the inside temperature going to about 215°. The condenser was then replaced and heating continued at this bath temperature for nine and one-half hours, the inside temperature remaining at 215–220°. If the inside temperature dropped below 215°, the condenser was again removed briefly. After the mixture had been cooled to about 100° it was diluted with 300 cc. of water containing 25 cc. of concentrated hydrochloric acid and extracted with three portions of pentane. The extracted material was carefully divided into acidic and neutral fractions as has been described above, and the acidic fraction was distilled at 1 mm. pressure to give a single fraction, XIV, as a colorless oil, b.p. 140.5–141°, weight 13.3 g. (89.9%), n_D^{20} 1.4465. For analysis there was used a center cut, b.p. 141°, n_D^{20} 1.4472.

Anal. Calc'd for $C_{18}H_{30}O_2$: C, 74.32; H, 12.48; eq. wt., 242.4.

Found: C, 74.17; H, 12.39; eq. wt. 241.5.

The *p*-bromoanilide was prepared by heating for one hour in 15 cc. of dry benzene a mixture of 2.0 g. of *p*-bromoaniline and 1.1 g. of acid chloride obtained from XIV with thionyl chloride. After the benzene solution had been washed with water, dilute hydrochloric acid, dilute sodium carbonate and water, the benzene was removed *in vacuo* and the residue crystallized from 10 cc. of nitromethane; m.p. of product, 87.5–88.9°. After two additional crystallizations from nitromethane there was obtained 0.6 g. of slender white needles, separating usually in burrs, m.p. 88.5–89.0°. This substance sinters very slightly at 86.5°, and if placed in a bath pre-heated to 87.7°, it melts completely at once except for a barely perceptible haze which disappears at 89.0°. Presumably, it is polymorphic.

Anal. Calc'd for $C_{21}H_{24}BrNO$: C, 63.62; H, 8.65.

Found: C, 63.51; H, 8.72.

The amide of XIV could not be obtained crystalline.

4-Butyl-4-ethylnonanoic acid (XV). The Wolff-Kishner reduction was carried out according to the above procedure, using 12.0 g. of pure keto ester, XIII. The product consisted of 4.5 g. (41.6%) of a slightly yellow oil, b.p. 139–143° (1.25 mm.), n_D^{20} 1.4544. For analysis, there was used a colorless sample of XV, obtained by saponification of its ester; b.p. 141.5° (1 mm.), n_D^{20} 1.4533.

Anal. Calc'd for $C_{18}H_{30}O_2$: C, 74.32; H, 12.48; eq. wt., 242.4.

Found: C, 74.09; H, 12.39; eq. wt. 245.7.

The *p*-bromoanilide prepared as described for its isomer, was obtained in 72% yield after one crystallization from hexane-acetone, m.p. 121–121.8°. After two additional crystallizations there were obtained fibrous white needles of the consistency of cotton, m.p. 121.6–122.2°.

Anal. Calc'd for $C_{21}H_{24}BrNO$: C, 63.62; H, 8.65.

Found: C, 63.95; H, 8.55.

The tribromoanilide of XV could not be obtained crystalline.

Separation of mixtures of acids XIV and XV. The data in the first three lines of Table I were obtained by separating the mixtures of XIV and XV which resulted from reduction of the mixed keto esters obtained from the cadmium reaction. Illustrative of this procedure is separation of 9.3 g. of mixed acids obtained by reduction of 15.5 g. of mixed keto esters. This mixture of keto esters was prepared according to Procedure (B) by the reaction of dibutylcadmium with the acid chloride from 14.6 g. of half ester, VIII.

The mixed acids (9.3 g.) were heated under reflux for two hours with 54 cc. (35 equivs.) of methanol and 2.35 cc. of concentrated sulfuric acid. The mixture was poured into 250 cc. of water and extracted with three portions of ether. After the extracts had been washed with water and dried, the solvent was flash-distilled and the residue distilled at 2 mm. pressure to give (a) 3.6 g. of the ester of XV, b.p. 121–121.5°, n_D^{20} 1.4437; (b) 0.1 g. of intermediate fraction; and (c) 5.3 g. of the acid, XIV, b.p. 148–152°, n_D^{20} 1.4475. Fraction (a), *methyl 4-butyl-4-ethylnonanoate*, was used for analysis.

Anal. Calc'd for $C_{18}H_{30}O_2$: C, 74.95; H, 12.58.

Found: C, 74.69; H, 12.38.

From the yield data obtained by reduction of the pure keto esters, it may be calculated that 1 g. of the ester of XV is obtained from 2.53 g. of the keto ester, XIII, while 1 g. of the acid, XIV, is obtained from 1.24 g. of the keto ester, XII. Thus, the amounts of Fractions (a) and (c) above indicate that the keto ester from which they were obtained consisted of 6.6 g. of XII and 9.1 g. of XIII, in reasonable agreement with the 15.5 g. of mixed keto ester actually reduced. Thus, the percentage of XII is calculated as 42%, and that of XIII as 58%.

In a similar manner were obtained the data on the composition of the keto ester obtained from the samples of distilled ester acid chlorides. These analyses are probably accurate to $\pm 2-3\%$.

Reaction of dibutylcadmium with α -butyl- α -ethylglutaric anhydride. A benzene (220 cc.) solution of dibutylcadmium prepared in the usual way from 55.4 g. of pure *n*-butyl bromide was treated with a solution of 20.0 g. of anhydride, VII, in 75 cc. of benzene, no heat being evolved during the addition. After the mixture had been heated under reflux, with stirring, for seven hours, it was decomposed with ice and dilute sulfuric acid. The organic phase was separated and the aqueous phase extracted with two portions of benzene. The combined benzene extracts were extracted with a mixture of 200 cc. of water, 60 cc. of methanol, and 20 cc. of 6 *N* sodium hydroxide. Using the methods described above, neutral material was extracted from the alkaline solution, which was then acidified and worked up to yield 22.9 g. of crude acidic material. This contained only 15.6 g. (60% yield) of keto acids, as shown by the analysis below.

The crude acidic material was heated under reflux for one and one-half hours with 85.5 cc. (24 equivs.) of methanol and 3.5 cc. of concentrated sulfuric acid. There was no darkening of the solution during heating. The mixture was poured into 350 cc. of water and extracted with three portions of pentane. The pentane solution was worked up as described above under "Separation of Keto Esters" to yield neutral and acidic fractions. The neutral fraction, on distillation at 1.5 mm. pressure, gave 11.3 g. of keto ester, XIII, b.p. 130.5–133°, n_D^{20} 1.4501.

The crude acidic fraction (8.5 g.) containing XVI, was subjected to the standard Wolff-Kishner reduction, and there was obtained 4.2 g. of the trialkylacetic acid, XIV, b.p. 145.5–146.5° (1.5 mm.), n_D^{20} 1.4483. This is equivalent to 4.9 g. of keto acid, XVI, or 5.2 g. of the ester, XII. Thus, the keto acid obtained from the cadmium reaction with the anhydride consisted of 31.5% of keto acid, XVI, and 68.5% of keto acid, XVII.

SUMMARY

1. The melting points of branched-chain acids are discussed and evidence is presented that no acid, except the iso acid, which contains a single branching methyl group can melt less than 10° below the normal isomer. Other branched-chain types which may be relatively high-melting are discussed.

2. A new synthesis of quaternary-carbon acids is developed and applied to the synthesis of *n*-butylethyl-*n*-heptylacetic acid and 4-butyl-4-ethylnonanoic acid.

3. It is shown that either of the ester acid chlorides related to the two half esters of α -butyl- α -ethylglutaric acid rearranges, on standing, to a mixture of the two isomeric ester acid chlorides.

4. Evidence is presented that dialkylcadmium reagents do not react with anhydrides by addition to the carbonyl group.

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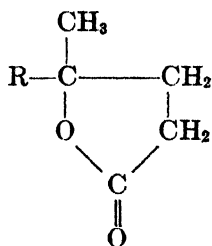
BRANCHED-CHAIN FATTY ACIDS. VII. SIMPLIFIED METHODS FOR PREPARING PURE BRANCHED- CHAIN ALCOHOLS AND HALIDES

JAMES CASON, PHYLLIS B. BREWER, AND ELDON L. PIPPEN

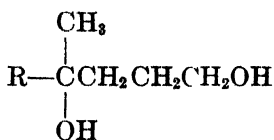
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In a previous paper (1) of this series, there was pointed out the undesirability of using secondary alkyl halides for preparation of pure branched-chain fatty acids. The threat of impurities arising from isomeric secondary halides is always present. A method was developed for obtaining branched-chain compounds from straight-chain starting materials involving the following steps: (a) preparation of a γ -alkyl- γ -valerolactone from a Grignard reagent and ethyl levulinate; (b) opening the lactone ring with thionyl chloride and converting the reaction product to an unsaturated ester; (c) hydrogenation to the saturated ester and, if desired, reduction to the alcohol. This method gave satisfactory yields of compounds of the desired purity; however, step (b) is rather laborious, so a study has been made of other methods of opening the lactone ring.

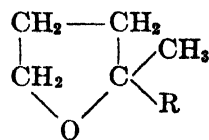
Although there have been several reports (2) of the Bouveault-Blanc reduction of lactones to glycols, none of the lactones reduced contained tertiary oxygen. This method of reduction has been found to proceed normally when applied to γ -*n*-butyl- γ -valerolactone (I) or γ -*n*-amyl- γ -valerolactone (II); however, the corresponding glycols, III and IV, were isolated in poor yield when the usual



I. R = *n*-C₄H₉
II. R = *n*-C₅H₁₁



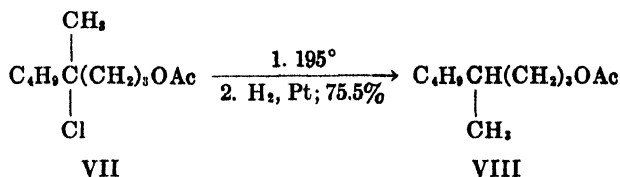
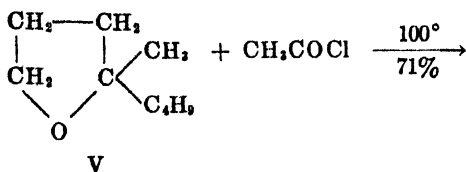
III. R = *n*-C₄H₉
IV. R = *n*-C₅H₁₁



V. R = *n*-C₄H₉
VI. R = *n*-C₅H₁₁

ratio of reagents (3) was used. By increasing the ratio of sodium to lactone by seventy-five per cent, the yield of glycol was raised to about 74%. Treatment of the diol with phosphorus tribromide leads to no recognizable products, and conversion of the diol to a branched-chain primary mono-alcohol was complicated by the fact that dehydration under mild conditions leads to a mixture of unsaturated alcohol and tetrahydrofuran (V or VI). The unsaturated alcohol may be converted readily into the saturated primary alcohol; however, conversion of the tetrahydrofuran to the primary alcohol proved rather tedious. Wilson (4) has recently made a study of the ring-opening of tetrahydrofurans and obtained relatively clean-cut results with hydrogen bromide in acetic acid or acetic anhydride in the presence of catalytic amounts of zinc chloride. A study of the opening of our 2,2-dialkyltetrahydrofurans indicates that acetyl

chloride with zinc chloride as catalyst (5) gives more clean-cut results than do the reagents studied by Wilson. The chief product from the tetrahydrofuran V is 1-acetoxy-4-chloro-4-methyloctane (VII).



Pyrolysis of the chloro ester, VII, at about 195° converts it to the unsaturated ester, which may be readily hydrogenated to the saturated ester, VIII. Saponification of VIII gave 4-methyl-1-octanol, identical with the sample obtained below by unequivocal procedures. The unsaturated ester was also obtained as one of the products of the reaction of acetic anhydride with V, and hydrogenation gave the saturated ester, VIII.

Although the above combination of reactions may be used to convert a lactone to the desired branched-chain primary alcohol, it is more laborious and less efficient than the previously-used method employing thionyl chloride; therefore, our investigation of the opening of lactone rings was continued by studying the catalytic hydrogenation of lactones I and II. Adkins and Folkers (6) hydrogenated γ -valerolactone over copper chromite catalyst at 250°, and obtained 78% yield of 1,4-pentanediol and 8% yield of *n*-amyl alcohol. When this procedure was applied to the tertiary lactones, I and II, there were obtained directly yields of 80–84% of the saturated mono-alcohols, 4-methyl-1-octanol and 4-methyl-1-nonanol. Since this represents the easiest and most efficient method yet discovered for converting a tertiary lactone to a primary mono-alcohol, its generality was further investigated by hydrogenating γ -ethyl- γ -valerolactone to 4-methyl-1-hexanol in 79–83% yield, and γ -*n*-hexyl- γ -valerolactone to 4-methyl-1-decanol in 82–88% yield. In order to obtain rapid hydrogenation and high yield, it is desirable to use a relatively high ratio of catalyst, for a mole equivalent of water is formed during the hydrogenation. A very small amount of the corresponding tetrahydrofuran was always obtained as a by-product.

γ -*n*-Butyl- γ -valerolactone was hydrogenated at lower temperatures in order to learn whether a better yield could be so obtained. Although the best yields of mono-alcohol were obtained at 250°, the results at lower temperatures are of considerable interest in connection with the mechanism of the hydrogenation and other products which may be obtained. In Table I are listed data concerning this reduction. In all runs there were used 20 g. of compound to be hydrogenated and 6 g. of copper chromite (7) catalyst, or else the same ratio in a

smaller run. The initial pressure at 23° was always in the range 2800–3000 lbs. per sq. in., and the final pressure was in the range 3600–4000 lbs.

Examination of the data in this table shows that at 250° the rate of hydrogenation of the lactone falls off sharply after hydrogenation is about 80% complete, indicating the possibility of two routes of hydrogenation. At 200° considerable glycol is obtained, in addition to mono-alcohol, and in the slow reaction at 150° the principal product obtained is glycol. Since the glycol is hardly attacked at 200°, and hydrogenated much more slowly than the lactone at 250°, it would seem that part of the mono-alcohol may be formed *via* the glycol (slow hydrogenation at end), but that the major portion must be formed at this temperature by some other route. The most obvious intermediate would appear to be the tetrahydrofuran, but this is eliminated by its exceedingly slow hydrogenation to give a poor yield of mono-alcohol. On the basis of the evidence available concerning

TABLE I
HYDROGENATION DATA

COMPOUND HYDROGENATED	TIME ^a , HOURS	TEMP., °C	PRODUCTS AND YIELDS, %		
			4-Methyl-1-octanol	Glycol, III	Tetrahydrofuran, V
Lactone, I	2.8 ^b	250	80.7	—	few
Lactone, I	7.5	200	39	28	few
Lactone, I	50	150	few	56.5	trace
Glycol, III	8	250	82.5	—	—
Glycol, III	3 ^c	200	5	68	trace
Tetrahydrofuran, V	20	250	27.3 ^d	—	17.6 ^d
4-Methyloctyl 4-methyloctanoate	2.2	250	88.6	—	—

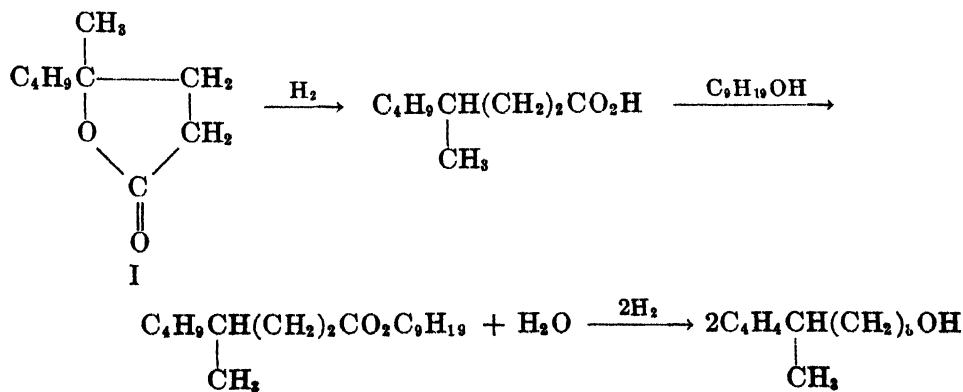
^a Time required, after heater and shaker were started, for maximum hydrogenation, as indicated by no further pressure drop. About seventy minutes were required for the temperature to reach 250°.

^b Hydrogenation was 80% complete after 1.6 hour.

^c Pressure drop was small.

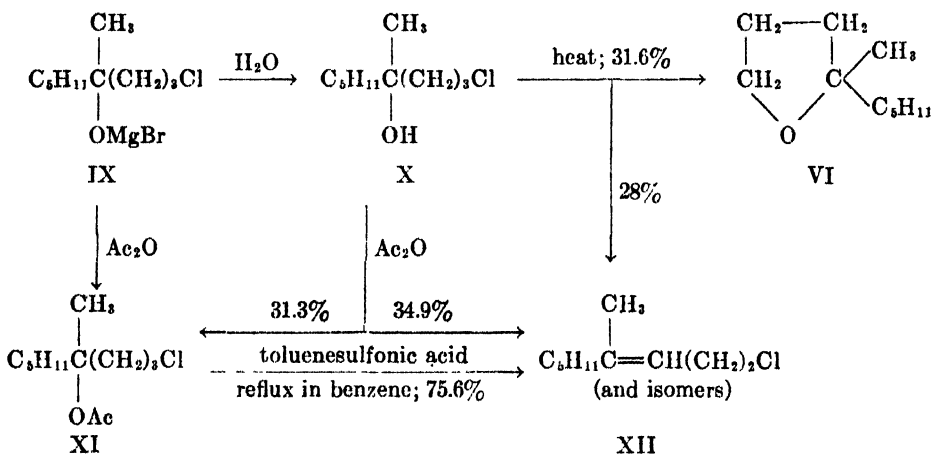
^d Nothing else was recovered.

the nature of the intermediates in the rapid hydrogenation of the lactone at 250°, the route indicated in the accompanying equation seems reasonable.



Formation of the acid might occur by direct hydrogenolysis or by hydrogenation of unsaturated acid in equilibrium with the lactone. Alcohol for conversion of acid to ester could be initially supplied by hydrogenation *via* the glycol, and would accumulate as hydrogenation progressed. In a hydrogenation of lactone I, at 250°, in which a poor grade of catalyst was used, the major product obtained was the ester, 4-methyloctyl 4-methyloctanoate. Hydrogenation¹ of this ester at 250°, with Adkins catalyst, proceeded more rapidly (*cf.* Table I) than hydrogenation of the lactone. This is reasonable, since the lactone is hydrogenated partly by the slower route involving the glycol. Since water is formed in hydrogenation of the lactone by any route, the rate would be expected to fall off rapidly at lower temperature where more time is available for deactivation of the catalyst by water. Also, the data indicate that rate of hydrogenolysis to glycol falls off much less rapidly with decreasing temperature and deactivation of catalyst than does the rate of hydrogenolysis by the route which gives ester. The failure to attain good material balance in all of these hydrogenations is attributed to chain cleavage to products of too low boiling point to be normally recovered.

Although the above methods make pure branched-chain alcohols readily available by a two-step procedure, it would seem possible to obtain the corresponding alkyl chloride still more readily by way of a Grignard reaction on the commercially available 5-chloro-2-pentanone. The initial reaction product expected from such a reaction, using *n*-amylmagnesium bromide, is represented by formula IX. Such a product appears to be obtained, and may be converted to the unsaturated chloride, XII, in a variety of ways, as shown in the chart.



All yields indicated in this chart are over-all yields based on 5-chloro-2-pentanone. The unsaturated chloride may be converted to 1-chloro-4-methylnonane in 75–80% yield by hydrogenation with platinum catalyst at low pressure and room temperature.

The chlorohydrin, X, may be obtained by decomposing the Grignard reagent

¹ We are indebted to Dr. F. B. Zienty for suggesting this interesting experiment.

with saturated ammonium chloride, but distillation of this substance without decomposition was not accomplished. Since pyrolysis gave a mixture of products and conversion of VI to desired compounds had been found difficult, dehydration with acetic anhydride was attempted but, surprisingly enough, about equal amounts of acetoxy chloride, XI, and unsaturated chloride, XII, were obtained. In the course of identification of the acetoxy chloride it was discovered that it may be converted in high yield to the unsaturated chloride by the procedure of Baumgarten and Hauser (8). Further, if the Grignard complex, IX, is decomposed with acetic anhydride, the acetoxy chloride is the principal product, and this may be converted directly, without isolation, to the unsaturated chloride. Thus, 1-chloro-4-methylnonane may be obtained from 5-chloro-2-pentanone in an over-all yield of 61%.

The synthesis of branched-chain acids from the alcohols and chloride described in this paper will be reported later.

EXPERIMENTAL

All boiling points are uncorrected. All distillations, unless otherwise specified, were carried out in a half-meter column containing a tantalum wire spiral of the Podbielniak type, and equipped with a heated jacket and partial reflux head. Microanalyses by C. W. Koch and V. H. Tashinian.

γ -Alkyl- γ -valerolactones were prepared according to the procedure (1) described for γ -*n*-propyl- γ -valerolactone, and the data on these compounds are found in Table II. The ethyl levulinate and alkyl bromides used as starting materials were distilled through the column and collected over ranges of about one degree.

4-Methyl-1,4-octanediol (III) was prepared by reduction of 52 g. (0.33 mole) of lactone I with 1 liter of anhydrous *n*-butyl alcohol and 60 g. (2.6 atoms) of sodium, according to the procedure of Reid *et al.* (3). After all the sodium had dissolved, 350 ml. of water was added and the mixture heated under reflux for thirty minutes to ensure saponification of any ester which may have been formed by trans-esterification of the lactone. The butanol layer was separated and the water layer extracted with 75 ml. of butanol. The residue obtained after distillation of the butanol was distilled at 4 mm. pressure. After a small fore-run, the colorless, viscous diol was collected at 125–126°, n_D^{20} 1.4540, wt. 32.3 g. (60.6%) [literature (9), b.p. 119° (3.5 mm.), n_D^{20} 1.4587].

There was about 20 g. of very viscous distillation residue which set to a glass on cooling. This proved to consist largely of the sodium salt of γ -hydroxy- γ -methylcaprylic acid. By solution in water, acidification, extraction with ether and distillation of the residue obtained from the extract, the lactone was recovered from this salt. When more sodium was used in the reduction, as described for the homolog below, there was very little of this residue.

4-Methyl-1,4-nonanediol (IV) was prepared as described for its homolog, III, except that the amount of sodium was increased to 2.93 atoms for 0.33 mole of lactone. This increased the yield of diol to 73.7%. After a small fore-run it was collected at 131–132° (5 mm.), n_D^{20} 1.4553.

Anal. Calc'd for $C_{10}H_{22}O_2$: C, 68.91; H, 12.73.

Found: C, 68.19; H, 12.65.

Dehydration of 4-methyl-1,4-octanediol. A mixture of 44.8 g. of the diol (III) and a few crystals of iodine was heated under the column in an oil-bath kept at 155–165°. Water was smoothly evolved and was removed by keeping the jacket temperature of the column at about 90°. If water is allowed to run back there is much sputtering and frothing. After water evolution had ceased (thirty to forty-five minutes), the organic layer was separated

from the small two-phase distillate and returned to the distillation flask. Distillation at 24 mm. pressure gave two main fractions: (a) b.p. 68–68.5°, n_D^{20} 1.4260, wt. 18.5 g.; (b) b.p. 109–110°, wt. 11.3 g.

Fraction a is *2-n-butyl-2-methyltetrahydrofuran* (V), and has a characteristic penetrating odor.

Anal. Calc'd for $C_7H_{10}O$: C, 76.00; H, 12.75.

Found: C, 75.54; H, 12.92.

Fraction b is *4-methyl-1-octanol*, and it was hydrogenated immediately at low pressure and room temperature in 125 ml. of 95% ethyl alcohol, using 0.25 g. of platinum oxide catalyst. Distillation yielded 9.2 g. of *4-methyl-1-octanol*, b.p. 104–105° (19 mm.), n_D^{20} 1.4309. [Literature (10, 11), b.p. 106° (17 mm.), n_D^{20} 1.4335.]

In another, smaller run, there was obtained 14.4 g. of tetrahydrofuran and 14.0 g. of unsaturated alcohol.

Dehydration of 4-methyl-1,4-nonanediol (21 g.) as described above gave 5.7 g. of *2-n-amyl-2-methyltetrahydrofuran* (VI), b.p. 75–77° (16 mm.), n_D^{20} 1.4314, and 5.7 g. of *4-methyl-1-nonenol*, b.p. 113–114° (16 mm.). A center cut of VI was used for analysis.

Anal. Calc'd for $C_{10}H_{20}O$: C, 76.86; H, 12.90.

Found: C, 76.80; H, 13.10.

TABLE II

 γ -ALKYL- γ -VALEROLACTONES

γ -VALEROLACTONE	B. P., °C	MM. HG	YIELD, %	n_D^{27}
γ -Ethyl- ^a	117–117.5	25	64	1.4380
γ -n-Butyl-	125–126 ^b	15	76	1.4410
γ -n-Amyl- ^c	130–132	9	71	1.4446
γ -n-Hexyl-	136–137 ^d	7.5	76	1.4470 ^d

^a This lactone boils only 11° above ethyl levulinate and was separated from this ester by distillation through a 1-meter packed column.

^b Wilson (ref. 11) gives b.p. 120–123° (15 mm.).

^c *Anal.* Calc'd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66.

Found: C, 70.56; H, 10.62.

^d Frank, Arvan, Richter, and Vanneman, *J. Am. Chem. Soc.*, **66**, 6 (1944), give b.p. 120–125° (4–5 mm.), n_D^{20} 1.4487.

The unsaturated alcohol was hydrogenated like its homolog in 150 ml. of 95% ethyl alcohol, using 0.1 g. of platinum oxide catalyst. Hydrogenation was complete in twenty minutes, and distillation of the product gave a 78% yield of *4-methyl-1-nonanol*, b.p. 111–112° (14 mm.), n_D^{20} 1.4333. [Literature (10), b.p. 120° (17 mm.), n_D^{20} 1.4364.] No solid derivative of this alcohol could be obtained, although the phenylurethan, α -naphthylurethan, and *p*-phenylbenzoate were prepared.

Reaction of 2-n-butyl-2-methyltetrahydrofuran with acetic anhydride. A mixture of 10 g. of V, 25 g. of acetic anhydride, and 0.2 g. of anhydrous zinc chloride was heated under reflux for twenty-four hours. After addition of five volumes of water the mixture was extracted with benzene three times. The extracts were washed with water, sodium bicarbonate solution, and water, then dried. The residue remaining after distillation of the solvent was distilled at 12 mm. pressure to give: (a) 5.45 g., b.p. 103°; (b) 1.06 g., b.p. 103–148°; (c) 3.17 g., b.p. 148°, n_D^{20} 1.4530. Fraction (a), which is *4-methyloctenyl acetate* was hydrogenated immediately at low pressure and room temperature with platinum oxide catalyst to yield 4.6 g. of *1-acetoxy-4-methyloctane*, b.p. 101° (12.5 mm.), n_D^{20} 1.4215. A center cut was used for analysis.

Anal. Calc'd for $C_{11}H_{22}O_2$: C, 70.91; H, 11.91.

Found: C, 70.69; H, 11.90.

This substance was shown to be the primary acetate, rather than the tertiary acetate, by its failure to lose acetic acid on heating in benzene with toluenesulfonic acid (8). The material recovered had the b.p. 102–103° (13.5 mm.) and n_D^{20} 1.422.

Fraction (c), above, has about the right boiling point for the diacetate of the diol, III; however, it failed to react with toluenesulfonic acid in boiling benzene (8), and the analytical values (C, 69.43, 69.51; H, 9.81, 9.80) are in disagreement with those calculated for the diacetate (C, 63.91; H, 9.90). The analytical values found give the improbable empirical formula, $C_9H_{14}O_2$, and this fraction may be an azeotrope.

Reaction of 2-n-amyl-2-methyltetrahydrofuran with hydrogen bromide in acetic acid. To 25 ml. of a 35.5% solution of anhydrous hydrogen bromide in glacial acetic acid was added 10 g. of VI, the addition causing no appreciable evolution of heat. After the mixture had been kept at room temperature for twenty-two hours it was diluted with four volumes of water and extracted with two portions of benzene. On attempted distillation of the residue from this extract, hydrogen bromide was lost; so the material was heated for one hour at 185–195°, and then distilled at 10 mm. pressure. This gave a principal fraction boiling at 90–93° and weighing 8.2 g. Hydrogenation at low pressure and room temperature in 75 ml. of 95% ethyl alcohol with 0.1 g. of platinum oxide catalyst resulted in absorption of one equivalent of hydrogen in about twelve minutes, and distillation of the product gave only 4.8 g. of material boiling at 75–103° (19 mm.). Redistillation gave 2.0 g. of material of b.p. 102.5–103.5°, n_D^{20} 1.4313. This substance is probably 1-acetoxy-4-methylnonane.

Anal. Calc'd for $C_{12}H_{24}O_2$: C, 71.94; H, 12.08.

Found: C, 72.41; H, 12.29.

The behavior of these reaction products during the work-up suggests a mixture of compounds resulting from different combinations of bromine and acetoxy on the primary and tertiary carbons, and since the reaction is so unpromising it was not further investigated.

Reaction of 2-n-butyl-2-methyltetrahydrofuran with acetyl chloride. A mixture was prepared of 11.7 g. (0.08 mole) of the tetrahydrofuran, V, about 0.1 g. of fused zinc chloride, and 0.1 mole of freshly distilled acetyl chloride. After a brief induction period the reaction became vigorously exothermic and cooling was necessary to keep it under control. After heat evolution had ceased (about five minutes) the dark red-brown mixture was heated under reflux on the steam-bath for one hour. After dilution of the cooled reaction mixture with water it was extracted with benzene, and the extract was washed with water, sodium bicarbonate solution, and water. After drying, the solvent was distilled and the residue distilled at 1.6 mm. pressure. After a fore-run of 0.9 g. the *chloro ester*, VII, was collected at 96–101°, wt. 12.9 g. (70.9%), n_D^{20} 1.4443. In order to avoid loss of hydrogen chloride from this compound, the bath temperature must not exceed about 130°. A center cut was used for analysis.

Anal. Calc'd for $C_{11}H_{21}ClO_2$: eq. wt., 110.4.

Found: eq. wt., 113.5, 113.0.

In order to prove the structure of VII, 10.4 g. (0.05 mole) was pyrolyzed at 190–200° for seventy-five minutes, the gas evolved giving a precipitate of silver chloride when absorbed in aqueous silver nitrate. On distillation of the pyrolysis product there was obtained 7.0 g. (80.5%) of unsaturated ester, b.p. 106.5–108.5° (25 mm.). This was hydrogenated immediately at low pressure and room temperature in 75 ml. of glacial acetic acid in the presence of 0.1 g. of platinum oxide catalyst, the theoretical quantity of hydrogen being consumed in ten minutes. Distillation at 19 mm. pressure gave 6.6 g. (93.5%) of 1-acetoxy-4-methyloctane (VIII), b.p. 110–111.5°, n_D^{20} 1.4209.

Anal. Calc'd for $C_{11}H_{22}O_2$: eq. wt., 186.3.

Found: eq. wt., 190.7, 191.2.

Saponification of this ester with alcoholic potassium hydroxide gave a 72% yield of 4-methyl-1-octanol, b.p. 111–111.5°, (24 mm.) n_D^{20} 1.4318.

Reaction of 2-n-amyl-2-methyltetrahydrofuran with acetyl chloride was carried out as described above for the lower homolog. From 9.0 g. (0.06 mole) of the tetrahydrofuran, VI, there was obtained 1.1 g. of the starting material (b.p. 48–49° at 1.5 mm. n_D^{20} 1.4299),

1.3 g. of intermediate fraction and 11.2 g. (82.0%) of 1-acetoxy-4-chloro-4-methylnonane, b.p. 101–105° (1.5 mm.) n_D^{25} 1.4452. A center cut was used for analysis.

Anal. Calc'd for $C_{13}H_{25}ClO_2$: Cl, 15.10; eq. wt., 117.4.

Found: Cl, 14.43, eq. wt., 120.3.

Hydrogenation of γ -alkyl- γ -valerolactones at 250°. In all hydrogenations, a steel bomb was charged with lactone and copper chromite (7) catalyst in the ratio of 20 g. of lactone to 6 g. of catalyst. The initial pressure at room temperature was in the range 2700–3100 lbs. per sq. in. Shaking and heating were started simultaneously, and hydrogen was absorbed rapidly above 200° so that the maximum pressure never exceeded about 4800 lbs. Shaking was continued until the pressure became constant, which occurred after 2.5–3.5 hours from the time heating was started. The pressure drop corresponded to 3.0–3.1 moles of hydrogen per mole of lactone. The product was washed out with acetone and distilled. Data on the products are given in Table III.

In one run with γ -*n*-hexyl- γ -valerolactone, only one-third as much catalyst was used as specified above. The time of hydrogenation was about 5.5 hours, but the yield of 4-methyl-1-decanol, b.p. 92–94° (3 mm.), was 82.5%, almost as high as obtained with the higher ratio of catalyst.

In all successful runs, catalyst prepared according to Adkins (7) was used. When Harshaw copper chromite catalyst (Cu-186-powder) was used, the hydrogenation did not

TABLE III
PREPARATION OF 4-METHYL-1-ALKANOLS BY LACTONE HYDROGENATION

ALCOHOL	B. P., °C	MM. HG	n_D^{25}	YIELD %
4-Methyl-1-hexanol	83–84	23.5	1.4223	79–83
4-Methyl-1-octanol	104–105	18	1.4320	77–81
4-Methyl-1-nonanol	115–116.5	17	1.4350	84
4-Methyl-1-decanol ^a	105–107	5	1.4375	82–88

^a Anal. Calc'd for $C_{11}H_{24}O$: C, 76.69; H, 14.04.

Found: C, 76.62; H, 14.00.

go to completion. In a run in which 30 g. of lactone I was reduced, the total recovery of products boiling above 44° (8 mm.) was as follows: (a) 6.6 g. of 4-methyl-1-octanol, b.p. 85.5–87.5° (6 mm.), n_D^{25} 1.4347; (b) 11.5 g. of 4-methyloctyl 4-methyloctanoate, b.p. 151–153.5° (4 mm.), n_D^{25} 1.4404, saponification equivalent, 276 (calc'd 284).

Data on hydrogenation of 4-methyloctyl 4-methyloctanoate are included in Table I. Properties of the resultant 4-methyl-1-octanol were, b.p. 110.5–111.5° (24 mm.), n_D^{25} 1.4340.

In all hydrogenations, the product contained 2–4% of material boiling below the alcohol and consisting largely of the tetrahydrofuran. In the case of the hexyl lactone, this fore-run was redistilled, and yielded 2-*n*-hexyl-2-methyltetrahydrofuran, b.p. 67° (5 mm.) n_D^{25} 1.4340.

Anal. Calc'd for $C_{11}H_{22}O$: C, 77.59; H, 12.98.

Found: C, 77.70; H, 13.08.

The fore-run from 4-methyl-1-nonanol consisted of 2-*n*-amyl-2-methyltetrahydrofuran, b.p. 77–80° (17 mm.), n_D^{25} 1.4307, these properties being in agreement with those of the sample obtained by dehydration of diol IV.

Hydrogenations carried out at 150° and 200° followed the same general procedure as those at 250°, and results are found in Table I.

Reaction of *n*-amylmagnesium bromide with 5-chloro-2-pentanone. (A) Preparation of 1-chloro-4-methylnonene (XII). A Grignard reagent was prepared in an atmosphere of nitrogen from 37.8 g. (0.25 mole) of purified *n*-amyl bromide and 5.34 g. (0.22 mole) of magnesium in 115 ml. of ether. As this stirred solution was cooled in an ice-salt bath there was added

24.1 g. (0.2 mole) of freshly-distilled 5-chloro-2-pentanone in 50 ml. of ether at as fast a rate (10-15 minutes) as consistent with keeping the temperature at 0° or less. After addition was complete stirring was continued at 0° for one hour, then there was added to the cold mixture, during about ten minutes, 61.2 g. (0.6 mole) of acetic anhydride. After this addition the cooling bath was removed and stirring continued for forty-five minutes as the mixture warmed up to room temperature (a precipitate separated during this period). After decomposition of the organometallic complex with ice and water, the ether layer was separated and dried, then solvent and acetic acid were distilled, the last traces *in vacuo*. The residue was heated under reflux for two hours with 1 g. of *p*-toluenesulfonic acid monohydrate and 100 ml. of dry benzene. The resultant solution was washed with enough sodium bicarbonate solution to remove acetic and *p*-toluenesulfonic acids, washed with water, and filtered through a layer of sodium sulfate. Distillation at 18 mm. pressure of the residue obtained from this solution gave 2.2 g. of fore-run, b.p. 55-98°, and 26.4 g. (75.6%) of 1-chloro-4-methylnonene, b.p. 98-100°, n_D^{25} 1.4524.

In several runs in which the Grignard solution was added to the chloro ketone solution, the yield was considerably lower than in the above-described procedure, and a large distillation residue was obtained. In one run, the Grignard reagent was decomposed with concentrated aqueous hydrochloric acid, in hopes of obtaining the 1,4-dichloride, which could be pyrolyzed to the desired product; however, the behavior on pyrolysis indicated that the tertiary hydroxyl had not been converted to chloride.

(B) *2-n-Amyl-2-methyltetrahydrofuran* (VI) and *1-chloro-4-methylnonene* (XII). The Grignard reaction between *n*-amylmagnesium bromide and the chloro ketone was run as above, and the complex was decomposed with 32 ml. of saturated ammonium chloride solution. The ether solution was decanted from the precipitated salts, and the salts washed with several portions of ether. The residue remaining after removal of solvent was pyrolyzed at 160-180° for three hours, then distilled. After a fore-run of 1.8 g., there was obtained 10.0 g. (31.6%) of *2-n*-amyl-2-methyltetrahydrofuran, b.p. 87.5-89.5° (28 mm.). After an intermediate fraction of 2.5 g. the unsaturated chloride was collected at 98-100° (20 mm.), wt. 10.0 g. (28%).

(C) *4-Acetoxy-1-chloro-4-methylnonane* (XI) and *1-chloro-4-methylnonene* (XII). The Grignard reaction was carried out and the complex decomposed with ammonium chloride as described under (B). After the ether solution had been dried overnight with calcium sulfate, 50 ml. of acetic anhydride was added, and solvent was distilled until the bath temperature reached 125°. After heating at this temperature had been continued for three hours, low-boiling material was removed *in vacuo* and the residue distilled to give two principal fractions: (a) 12.2 g. (34.9%) of unsaturated chloride, b.p. 97.5-101.5° (17 mm.); (b) 14.7 g. (31.3%) of 4-acetoxy-1-chloro-4-methylnonane, b.p. 141-143° (17 mm.). A center cut of the acetoxy chloride, b.p. 141.5-141.7° (18 mm.) n_D^{25} 1.4442, was used for analysis.

Anal. Calc'd for $C_{13}H_{23}ClO_2$: C, 61.39; H, 9.87; Cl, 15.10.

Found: C, 61.54; H, 9.86; Cl, 15.55.

When the acetoxy chloride was treated with *p*-toluenesulfonic acid as described under (A), it was converted in 86% yield to the unsaturated chloride, b.p. 97-100° (17 mm.).

1-Chloro-4-methylnonane. In a typical run, 15.1 g. of freshly distilled unsaturated chloride was hydrogenated at low pressure and room temperature in 150 ml. of 95% ethyl alcohol with 0.1 g. of platinum oxide. Hydrogenation was complete in fifteen minutes, and distillation of the product gave 12.3 g. (80.7%) of the saturated chloride, b.p. 103-104.5° (21 mm.), n_D^{25} 1.4362.

Anal. Calc'd for $C_{10}H_{21}Cl$: C, 67.96; H, 11.97; Cl, 20.06.

Found: C, 68.00; H, 12.00; Cl, 19.87.

SUMMARY

Several γ -alkyl- γ -valerolactones have been prepared and it has been shown that they may be converted to 4-alkyl-1-alkanols in yields of 80-88% by high pressure hydrogenation over copper chromite catalyst.

1,4-Glycols may be obtained by reduction of such lactones with sodium and alcohol; however, conversion of the glycols to unsaturated mono-alcohols is difficult on account of tendency toward tetrahydrofuran formation.

Ring opening of 2-alkyl-2-methyltetrahydrofurans with acetic anhydride, acetyl chloride, and hydrogen bromide in acetic acid has been studied. Acetyl chloride was the most satisfactory reagent as regards better yield of a single product.

The reaction between *n*-amylmagnesium bromide and 5-chloro-2-pentanone has been studied and a method developed for obtaining 1-chloro-4-methylnonene in good yield. Under other conditions there may be obtained products consisting in part of 4-acetoxy-1-chloro-4-methylnonane or 2-*n*-amyl-2-methyltetrahydrofuran.

BERKELEY, CALIFORNIA

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CERTAIN METAL DERIVATIVES OF 2,4-PENTANEDIONE¹

LEWIS F. HATCH AND GORDON SUTHERLAND

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In the course of a research program in this Laboratory it became necessary to prepare several metal derivatives of 2,4-pentanedione (acetylacetone) and to determine their solubilities in different types of hydrocarbons. A survey of the literature indicated that the metal derivatives were usually prepared by a reaction between metal hydroxides (1, 2, 3, 4, 5) or carbonates (3, 5, 6, 7) and the enol form of the pentanedione. The metals (8), metal oxides (9), chlorides (5, 10), and acetates (11) have also been used, as well as the double decomposition of an alkali or ammonium salt of pentanedione and a metal salt (12, 13, 14). Although appreciable work has been reported on compounds of this type, only generalizations have been made regarding their solubilities, densities, and melting points.

The sodium, potassium, magnesium, beryllium, and aluminum derivatives of 2,4-pentanedione have now been prepared and their melting points and densities determined. These compounds were prepared from either the corresponding hydroxide or by direct action of the pentanedione on the metal. In each case the previously reported techniques have been modified and very good yields were obtained.

The ultraviolet absorption spectra of the compounds have also been obtained and these data (Figure 1) show that the order of increasing amplitude of absorption is sodium, potassium, magnesium, beryllium, and aluminum. From the general chemical characteristics of these metals it might be expected that the sodium, potassium, and magnesium compounds would have the properties of a salt and the beryllium and aluminum compounds would have the properties of a chelate compound. Because the greatest absorption is caused by the organic portion of the molecule, the molecules with the largest number of pentanedione units might be expected to have the greatest absorption. The chelate bond will also increase the absorption and accounts for the greater amplitude of the beryllium compound over that of the magnesium salt.

n-Hexane, cyclohexane, and benzene have been used as the solvents in the solubility determinations of the various compounds, because they represent the three types of hydrocarbons which would be present in petroleum. Compounds with the same number of carbon atoms were used to prevent any differences in solubility caused by large differences in molecular weight. Only the beryllium and aluminum compounds showed appreciable solubility and they were extensively soluble only in benzene (Figure 2). This solubility behavior might be expected because of the chelate structure of the beryllium and aluminum com-

¹ The work described in this article was done at the Defense Research Laboratory of The University of Texas. This Laboratory operates under Contract NOrd-9195 between The University of Texas and the Bureau of Ordnance of the Navy Department.

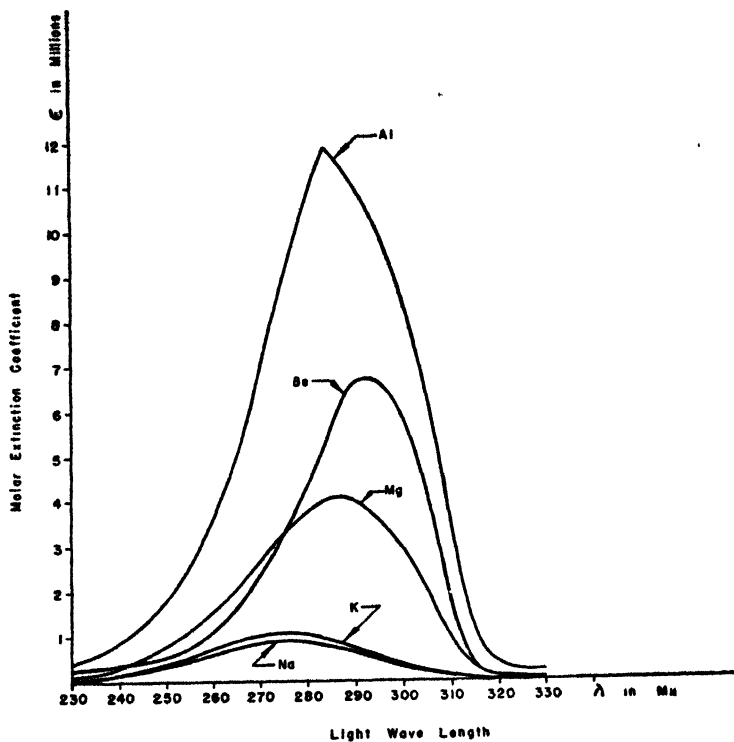


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA OF CERTAIN METAL DERIVATIVES OF 2,4-PENTANEDIONE

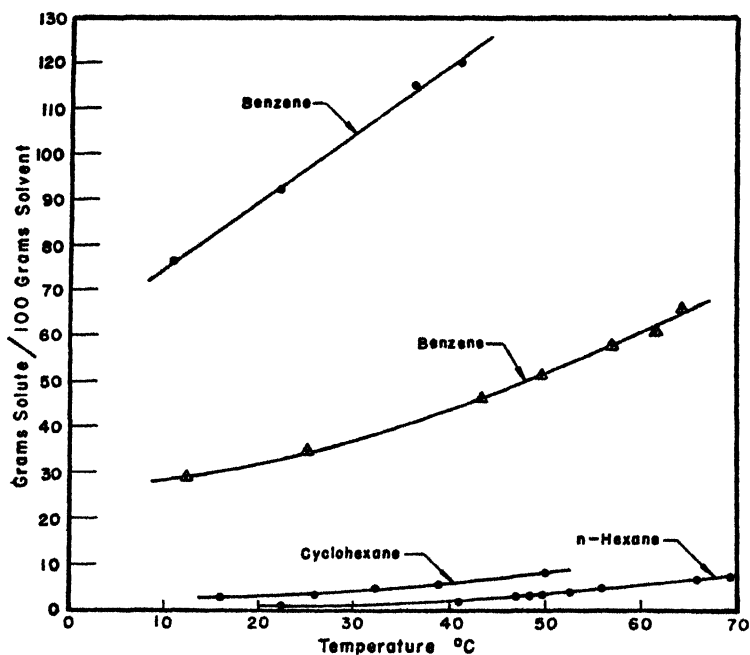


FIG. 2. SOLUBILITY OF BIS(2,4-PENTANEDIONO)BERYLLIUM AND TRIS(2,4-PENTANEDIONO)ALUMINUM IN BENZENE, CYCLOHEXANE AND *n*-HEXANE. o, BIS(2,4-PENTANEDIONO)BERYLLIUM; Δ, TRIS(2,4-PENTANEDIONO)ALUMINUM

pounds. The sodium, potassium and magnesium salts are essentially insoluble in these hydrocarbons.

EXPERIMENTAL

All melting points are corrected.

Materials. The pentanedione was obtained from Carbide and Carbon Chemicals Corp., New York. It was purified by fractional distillation and the material boiling between 140–140.5° was used.

The *n*-hexane and cyclohexane used as solvents were obtained from Phillips Petroleum Company, Bartlesville, Oklahoma. The *n*-hexane contained 95 mole per cent *n*-hexane and 4 mole per cent methylcyclohexane. The cyclohexane was of 99 mole per cent minimum purity. The benzene was of reagent grade.

All the inorganic reagents in this investigation were of C. P. or reagent grade.

Sodium 2,4-pentanedionate. Sodium 2,4-pentanedionate was prepared both by the reaction between sodium hydroxide and the pentanedione in either water or ethanol and by the direct action of sodium metal in toluene on the pentanedione. In the first method 100 g. (1.0 mole) of pentanedione was slowly added to 40 g. (1.0 mole) of sodium hydroxide while maintaining the temperature below 70°. When concentrated solutions of sodium hydroxide were used, the product crystallized when the reaction mixture cooled; yield 98 g. (80%).

Ethanol as the solvent gave the same yield but without the necessity of such close temperature control as with water as the solvent. In previously reported preparations of the salt from sodium hydroxide, solid sodium hydroxide was used and considerable trouble was encountered by the salt coating the sodium hydroxide.

In the second method of preparation 50 g. (0.5 mole) of pentanedione was added to 11.5 g. (0.5 mole) of sodium in 100 ml. of toluene. The temperature was maintained at 100° to keep the sodium molten; yield 101 g. (83%). When lower temperatures and solid sodium were used, salt coated the metal, causing a slower reaction and lower yields.

The sodium 2,4-pentanedionate was recrystallized from ethanol and its melting point determined in soft glass melting point tubes. When the melting point tube was slowly heated to the temperature at which the salt melted, the salt charred considerably. However, if the melting point tube was placed in the bath at about five degrees below the melting point of the salt and then the temperature slowly raised, a fairly sharp and reproducible melting point could be obtained with very little decomposition. This same procedure was also used to determine the melting points of the potassium and magnesium salts.

The density of the sodium salt was calculated from the specific gravity. The specific gravity was determined by the use of a specific gravity balance (gravitometer). The suspending liquid was pure *n*-heptane. This same method was used for the other four compounds with the exception of bis(2,4-pentanediono)beryllium where water was used as the suspending liquid.

It was not possible to obtain a satisfactory carbon analysis for the sodium, potassium, and magnesium salts. For this reason the percentage of metal was determined. Concentrated sulfuric acid was used to decompose the pentanedionate to the metal sulfate. The reaction mixture was heated to dryness over a microburner. The residue was then placed in a furnace and heated to red heat for one-half hour. After cooling, sulfuric acid was again added and the heating process repeated for five minutes in the furnace. The percentage of metal was calculated from the sulfate formed by the foregoing treatment; melting point 217–219°; d_4^{20} 1.213.

Anal. Calc'd for $\text{NaC}_5\text{H}_7\text{O}_2$: H, 5.78; Na, 18.84.

Found: H, 5.58; Na, 18.31.

Potassium 2,4-pentanedionate. The potassium 2,4-pentanedionate was prepared by the same two methods as used for the preparation of the sodium salt. Essentially the same yields were obtained; melting point 261–263°; d_4^{20} 1.216.

Anal. Calc'd for $\text{KC}_6\text{H}_7\text{O}_2$: H, 5.11; K, 28.30.

Found: H, 5.28; K, 27.79.

Magnesium 2,4-pentanedionate. Magnesium 2,4-pentanedionate was prepared by the action of magnesium metal on pentanedione. Two hundred grams (2 moles) of pentanedione in twice its volume of 70% ethanol was added to 48.6 g. of magnesium turnings. A vigorous reaction took place at 60–70° with the evolution of hydrogen. The magnesium 2,4-pentanedionate crystallized from the reaction mixture on cooling; yield 231 g., 93.6%; melting point 265–267°; d_4^{20} 1.162.

Anal. Calc'd for $\text{Mg}(\text{C}_6\text{H}_7\text{O}_2)_2$: H, 6.35; Mg, 10.92.

Found: H, 6.59; Mg, 10.62.

Bis(2,4-pentanediono)beryllium. Basic beryllium carbonate was treated with hot concentrated sulfuric acid to convert the carbonate to the sulfate. The beryllium sulfate was then dissolved in boiling water; and, after cooling, an equivalent amount of sodium hydroxide was added to form beryllium hydroxide. Two hundred grams (2 moles) of 2,4-pentanedione in an equal volume of benzene was refluxed for one hour with 43 g. (1 mole) of the beryllium hydroxide. The water which formed was separated from the benzene layer and the bis(2,4-pentanediono)beryllium crystallized from the benzene upon cooling; yield 172 g., 83%; melting point 108–109° [lit. (13) 108.5–109°]; d_4^{20} 1.108 [lit. (6) 1.168].

Anal. Calc'd for $\text{Be}(\text{C}_6\text{H}_7\text{O}_2)_2$: C, 57.96; H, 6.82; Be, 4.35.

Found: C, 58.21; H, 6.56; Be, 4.08.

Tris(2,4-pentanediono)aluminum. One hundred fifty grams (1.5 moles) of 2,4-pentanedione in an equal volume of benzene was added to an aqueous solution of 66.6 g. (0.5 mole) of aluminum chloride. The mixture was stirred and heated to reflux temperature. Sixty grams of sodium hydroxide (50% solution) was then added to the mixture. Sodium pentanedionate formed in the benzene layer but disappeared immediately because of the formation of the benzene-soluble tris(2,4-pentanediono)aluminum. The total reaction time was one-half hour. The reaction between 2,4-pentanedione and either aluminum chloride or hydroxide requires from one to three hours to go to completion. The compound was purified by crystallization from benzene; yield 143 g., 89%; melting point 193–194° [lit. (13) 194.6°]; d_4^{20} 1.204.

Anal. Calc'd for $\text{Al}(\text{C}_6\text{H}_7\text{O}_2)_3$: C, 55.52; H, 6.54; Al, 8.32.

Found: C, 55.58; H, 6.78; Al, 8.01.

Ultraviolet absorption. A Beckman Quartz Spectrophotometer was used to determine the ultraviolet absorption curves (Figure 1) for the compounds in ethanol.

Solubilities. The solubilities of these compounds were determined in the following manner. Known weights of the solvent and solute were placed in a 1 x 8 inch test tube equipped with a stopper holding a thermometer and a manually operated wire loop stirrer. The tube and its contents were heated until the solid dissolved. These were then cooled until crystals reappeared. On slow, careful reheating, with constant stirring, the temperature was noted at which the last crystals dissolved. This temperature could be reproduced within $\pm 0.5^\circ$. Each value plotted in Figure 2 is the average of several determinations.

The solubility of sodium, potassium, and magnesium pentanedionates is less than 0.01 g. in 100 g. of benzene, cyclohexane, and *n*-hexane at 70°. Tris(2,4-pentanediono)aluminum was soluble in both cyclohexane and *n*-hexane to the extent of less than 0.01 g. in 100 g. of solvent at 70°.

SUMMARY

1. The following metal derivatives of 2,4-pentanedione were prepared and characterized more completely than previously: Sodium 2,4-pentanedionate, potassium 2,4-pentanedionate, magnesium 2,4-pentanedionate, bis(2,4-pentanediono)beryllium, and tris(2,4-pentanediono)aluminum.

2. The ultraviolet absorption spectra of these compounds were obtained, as well as their solubility in benzene, cyclohexane, and *n*-hexane.

AUSTIN 12, TEXAS

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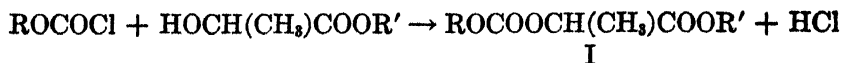
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MIXED ESTERS OF LACTIC AND CARBONIC ACIDS. REACTION OF CHLOROFORMATES WITH ESTERS OF LACTIC ACID

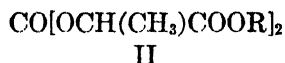
C. E. REHBERG, MARION B. DIXON, AND C. H. FISHER

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Although many esters of lactic acid have been described (1-3), and some of them have been acylated with various acid chlorides and anhydrides (1-9), few of the carbonates (I) have been reported. Since several alkyl chloroformates are now readily available, and esters of lactic acid are becoming increasingly important commercially (10-12), the preparation and study of additional mixed carbonic esters (I) of alkyl lactates appeared to be of interest.



Ritchie (4) and Kolfenback (13) treated methyl lactate with phosgene² and with methyl chloroformate and pyrolyzed the products [bis-(carbomethoxyethyl) carbonate (II, R = Me) and methyl carbomethoxyethyl carbonate, respectively] to make methyl acrylate. Both bis-(carbomethoxyethyl) carbonate [II, R = Et (90% yield)] and carbomethoxyethyl chloroformate have been prepared from ethyl lactate and phosgene (7, 14). Muskat and Strain (15) used the reaction between allyl or methallyl chloroformate and allyl, methallyl, or vinyl lactate to prepare several polymerizable carbonates (I, R and R' = alkenyl). Bis-(carbalkenoxyethyl) carbonates (II, R = alkenyl) also were prepared (16), starting with alkenyl lactates and phosgene.

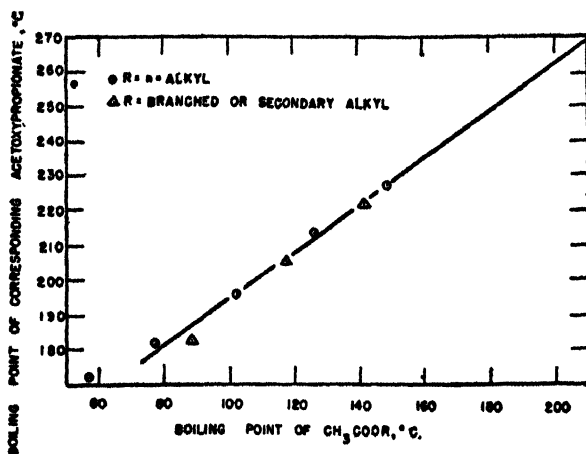


Fischer (17) and Freudenberg (18) and their co-workers prepared several methyl and ethyl carbonate derivatives, respectively, of lactic acid. Carbonates of α -hydroxy acids other than lactic acid also have been made (19, 20).

In the present work, the carbonates (Table I) were made by treating an hydroxy ester, usually a lactate, with a chloroformate. In some experiments an alkyl glycolate or α -hydroxyisobutyrate was used instead of a lactate. The lactates and glycolates were observed to undergo acylation more readily than the alkyl α -hydroxyisobutyrate. All the resulting carbonates were clear, colorless, mobile liquids having relatively low vapor pressures and, in general, good chemical and thermal stability.

¹ One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

² The unidentified product (boiling point 197-200°) obtained by Ritchie (4) by treating methyl lactate with phosgene appears from its physical constants and analytical data to be methyl carbomethoxyethyl carbonate (I, R, and R' = Me). This product might have been formed from methyl lactate and methyl chloroformate; methanol, a possible precursor of methyl chloroformate, might have resulted from the hydrolysis or auto-alcoholysis of methyl lactate.



Their polymers, presumably cross-linked, were clear, colorless, hard, insoluble, and infusible.

Drake and Carter (23) observed that certain alkyl and alkoxyethyl carbonates are compatible with cellulose acetate, and pointed out that the carbonates

TABLE I
 α -CARBALKOXYALKYL CARBONATES [DERIVATIVES OF LACTIC ACID,
(ROCOOCH(CH₃)COOR', UNLESS OTHERWISE INDICATED)]

NO.	R	R'	YIELD, %	n_D^{20}	d_4^{20}	ANALYSIS ^a					
						Mol. refr.		Carbon, %		Hydrogen, %	
						Calc'd	Found	Calc'd	Found	Calc'd	Found
1	Ethyl	Octyl	49	1.4281	.9846	71.80	71.70	61.26	61.28	9.55	9.61
2	Chloroethyl	Methyl	44	1.4392	1.2568	44.34	44.09	39.92	39.88	5.27	5.20
3	Ethyl	Allyl	40	1.4280	1.0776	48.25	48.28	53.46	53.53	6.98	7.07
4	Allyl	Allyl	64	1.4410	1.0790	52.40	52.43	56.07	56.14	6.59	6.58
5	Allyl	3-Buten-2-yl	75	1.4380	1.0608	57.02	56.47	57.89	57.48	7.06	7.12
6	Ethyl	β -Ethoxyethyl	42	1.4229	1.0791	54.97	55.30	51.28	51.32	7.75	7.87
7	Ethyl	β -Chloroethoxyethyl	68	1.4439	1.1923	59.84	59.86	44.70	44.67	6.38	6.43
8	Ethyl	β -Butoxyethyl	69	1.4268	1.0481	64.21	64.24	54.94	54.64	8.46	8.45
9	Ethyl	Cyclohexyl	36	1.4436	1.0743	60.47	60.36	58.98	58.75	8.25	8.19
10	Ethyl	Methylcyclohexyl	48	1.4422	1.0492	65.09	65.16	60.43	60.40	8.59	8.61
11	Ethyl	Tetrahydrofurfuryl	85	1.4434	1.1390	57.39	57.37	53.64	53.24	7.37	7.28
12 ^b	<i>n</i> -Butyl	<i>sec.</i> -Butyl	82	1.4221	1.0206	57.95	57.96	56.87	56.71	8.68	8.02
13 ^b	<i>n</i> -Amyl	Ethyl	78	1.4239	1.0442	53.33	53.31	55.04	54.99	8.31	8.18
14 ^c	<i>n</i> -Butyl	Ethyl	40	1.4202	1.0162	57.95	57.88	56.88	57.18	8.68	8.76
15 ^c	<i>n</i> -Amyl	Ethyl	29	1.4237	1.0038	62.57	62.57	58.51	58.25	8.28	9.01
16	<i>i</i> -Propyl	Methyl	35	1.4118	1.0734	44.10	44.07	50.52	50.16	7.42	7.42
17	<i>i</i> -Butyl	Methyl	84	1.4180	1.0549	48.71	48.73	52.93	52.76	7.90	8.06
18 ^d	Diethylene glycol	Ethyl	86	1.4407	1.1882	87.63	87.59	48.73	48.52	6.65	6.86
19 ^e	Diethylene glycol	<i>n</i> -Butyl	75	1.4428	1.1270	106.11	105.92	53.32	53.07	7.61	7.61

^a We are indebted to C. O. Willits and C. L. Ogg of the Analytical and Physical Chemistry Division for analytical data.

^b Derivative of glycolic acid, *i.e.*, ROCOOCH₂COOR'

^c Derivative of α -hydroxyisobutyric acid, *i.e.*, ROCOOC(CH₃)₂COOR'.

^d Diethylene glycol bis-(α -carbethoxyethyl carbonate).

^e Diethylene glycol bis-(α -carbobutoxyethyl carbonate).

examined by them might be useful as plasticizers. In making a brief study of the suitability of our carbonates as plasticizers, we determined compatibility with some of the commercial resins (Table II). Several of the carbonates were compatible with polymethyl acrylate, Vinylite VYHH, low-acetyl cellulose acetate, and ethylcellulose, but in general they were incompatible with high-

acetyl cellulose acetate and polyvinyl chloride. The tetrahydrofurfuryl ester was compatible with all the resins studied except polyvinyl chloride.

The stability to boiling water of some of the carbonates was determined by the method of Fordyce and Meyer (24). The two chlorine-containing esters (Table II) were least stable, presumably owing to the formation and catalytic action of

TABLE II
COMPATIBILITY AND BOILING WATER STABILITY DATA

ESTER NO. ^b	COMPATIBILITY WITH RESINS ^a						FREE ACIDITY ^h	BOILING WATER STABILITY ⁱ
	Cellulose acetate ^c		Ethyl- cellulose ^d	Vinylite VYHH ^{e, g}	Vinylite QYNA ^{d, f}	Polymethyl acrylate ^{e, g}		
	Low- acetyl	High- acetyl						
1		CI	CI	C	I	C	0.48	0
2	C	C	C	C	I	C	0.35	573.6
5		I	CI	CI	—	—	—	—
6	C	CI	—	—	—	—	—	—
7	C	CI	CI	C	I	C	2.59	203.1 ^j
8	C	CI	C	C	I	C	5.96	21.4 ^j
9	C	I	C	C	CI	C	7.90	2.85
10	I	CI	C	CI	CI	C	0.27	0.08
11	C	C	C	C	I	C	2.47	107.6 ^j
12	CI	I	CI	C	CI	C	0.18	0.33
13	I	I	C	C	CI	C	0.25	1.50
15	I	I	C	C	—	—	—	—
18	C	C	I	C	I	C	0.60	53.4
19	C	C	I	C	I	C	0.96	61.5

^a C = compatible; I = incompatible; CI = borderline compatibility.

^b Numbers are those used in Tables I and III.

^c Twenty per cent plasticizer.

^d Forty per cent plasticizer.

^e Copolymer (88–90% vinyl chloride and 12–10% vinyl acetate); the use of specific brands of commercial products should not be construed as an endorsement or recommendation of these products over similar materials not mentioned.

^f Polyvinyl chloride.

^g Emulsion polymerized.

^h Reported as the ml. *N* NaOH required to neutralize 100-g. sample.

ⁱ Difference between free acidity (footnote h) and the *N* NaOH required to neutralize 100-g. sample after boiling with water for 24 hours.

^j End point of titration uncertain because of fading.

hydrochloric acid. Some of the esters of ether-alcohols were relatively unstable to boiling water. The carbonates containing relatively little oxygen were most stable.

Boiling points at 760 mm. of the carbonates were estimated from the determined boiling point at 10 mm. and by other methods (Table III). Comparison of these boiling points with those of widely used plasticizers³ shows that some

³ For example, methyl and butyl phthalate boil at 150° and 200°, respectively, under 10 mm. pressure (25, 38).

of the carbonates are sufficiently nonvolatile for use as plasticizers. Compounds 18 and 19 (Tables I to III), prepared by acylating ethyl and butyl lactate with diglycol chloroformate $[O(CH_2CH_2OCOC l)_2]$, are of particular interest from the standpoint of low vapor pressure.

TABLE III
BOILING POINTS AND VISCOSITIES OF $ROCOOCH(CH_2)COOR'$

ESTER NO. ^a	R	R'	BOILING POINT, °C.				VISCOSITY AT 20°C.	
			10 mm. (determined)	760 mm. (est.)			Centi-stokes	Centi-poise
				A ^b	B ^c	C ^d		
1	Et	Octyl	168	312	295	317	8.96	9.10
2	$ClCH_2CH_2$	Me	136	272	—	—	28.82	22.93
3	Et	Allyl	111	240	231	229	—	—
4	Allyl	Allyl	125	258	—	244	—	—
5	Allyl	3-Buten-2-yl	126	259	—	257	—	—
6	Et	$EtOCH_2CH_2$	139	276	261	264	—	—
7	Et	$ClCH_2CH_2OCH_2CH_2$	176	323	296	—	26.21	21.98
8	Et	$BuOCH_2CH_2$	159	301	281	297	9.70	9.26
9	Et	Cyclohexyl	151	291	274	291	21.24	19.77
10	Et	Me cyclohexyl	157	298	278	307	20.39	19.43
11	Et	Tetrahydrofurfuryl	162	305	285	284	22.86	20.07
12 ^e	Bu	sec.-Bu	135	270	—	272	6.75	6.67
13 ^e	Am	Et	139	275	—	265	6.36	6.09
14 ^f	Bu	Et	120	251	—	252	—	—
15 ^f	Am	Et	131	265	—	273	—	—
16	Isopropyl	Me	100	226	—	211	—	—
17	Isobutyl	Me	110	238	—	233	—	—
18	Diethylene glycol	Et	258	427	—	410	221.7	263.4
19	Diethylene glycol	Bu	278	453	—	459	133.6	150.6

^a Numbers are those used in Tables I and II.

^b Estimated from the boiling point at 10 mm., using the equation, b.p. at 760 mm. = 1.276 (b.p. at 10 mm.) + 98, and the group 3 classification of C. Bordenca (26). Boiling points about 4° lower than those of Column A would be obtained by using Bordenca's group 4 classification.

^c The boiling point of $CH_3COOCH(CH_2)COOR$ (taken from Fig. 1) was used with Fig. 2 to estimate the boiling point of $CH_3CH_2OCOCH(CH_2)COOR'$ (See experimental section for further details).

^d Estimated by C. R. Kinney's method (27, 28).

^e Derivative of glycolic acid.

^f Derivative of hydroxyisobutyric acid.

Although the agreement among the estimated boiling points in Table III is unsatisfactory in some instances, estimated boiling points should be frequently useful for predicting whether proposed plasticizers would be too volatile.

A straight line was obtained by plotting the boiling points at 10 mm. of the carbonates



III

against the normal boiling points of the corresponding alcohols, that is, ROH (Fig. 3). A somewhat similar relationship, which appears to be applicable to all the carbonates (I), is shown in Figure 4. The relationships of Figures 3 and

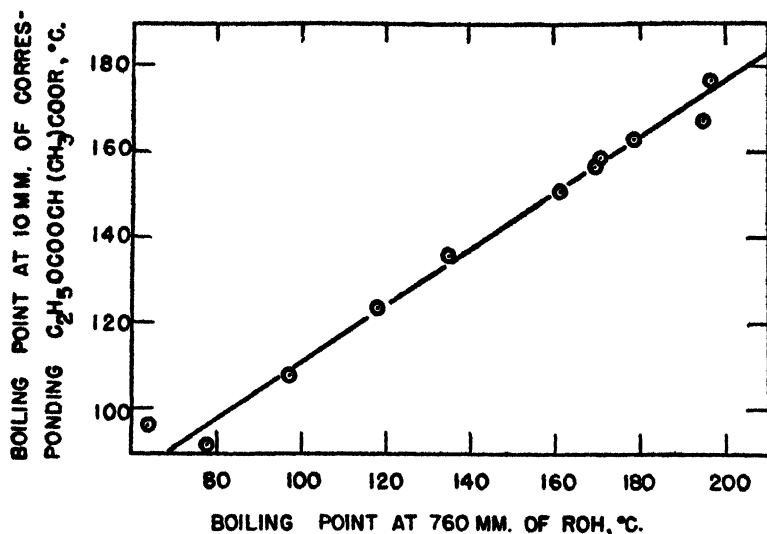


FIG. 3. RELATION BETWEEN BOILING POINTS OF ROH AND CORRESPONDING $C_2H_5OCOOCH(CH_3)COOR$

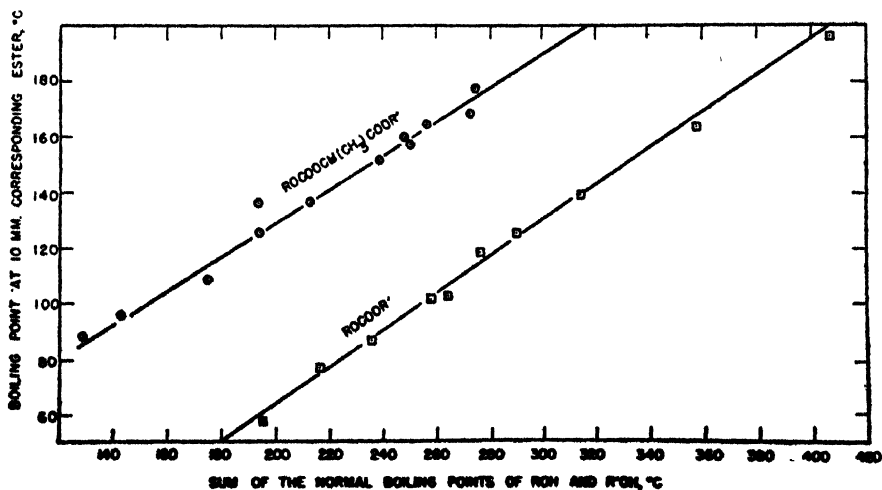


FIG. 4. RELATION BETWEEN THE SUM OF THE NORMAL BOILING POINTS OF ROH AND R'OH AND THE BOILING POINT AT 10 MM. OF THE CORRESPONDING $ROCOCOOCH(CH_3)COOR'$ OR $ROCOOR'$

4 should be useful for predicting the boiling points of other alkyl carbalkoxyethyl carbonates. Figure 4 indicates also that the effect of the lactic acid segment $[-OCH(CH_3)CO-]$ in alkyl carbalkoxyethyl carbonates is to raise the boiling point approximately 60° .

The viscosity of the carbonates (Table III) varied over a wide range, the compounds containing chlorine, rings, or two carbonate groups being relatively viscous.

ACKNOWLEDGMENT

We are indebted to U. S. Industrial Chemical Company for furnishing ethyl chloroformate, to Pittsburgh Plate Glass Company, Columbia Chemical Division, for allyl chloroformate, diethylene glycol bis-chloroformate, and technical, undistilled diglycol carbonate of butyl lactate, to Carbide & Carbon Chemicals Corporation for Cellosolve, Butyl Cellosolve, and diglycol chlorohydrin, to Rohm and Haas Company for ethyl α -hydroxyisobutyrate, and to the Barrett

TABLE IV
LACTIC ESTERS

ESTER	YIELD, %	BOILING POINT		n_D^{20}	d_4^{20}	MOLECULAR REFRACTION		SAP. EQUIV.	
		°C.	mm.			Calc'd	Found	Calc'd	Found
<i>n</i> -Octyl ^a	52	78	0.1	1.4350	0.9362	56.18	56.38	202.3	202.1
3-Buten-2-yl.....	77	70	13	1.4326	1.0091	37.24	37.10	144.2	144.5
Chloroethoxyethyl...	90	101	0.6	1.4565	1.2088 ^b	44.22	44.26	98.3	98.9 ^b
Tetrahydrofurfuryl...	94	80	1.1	1.4570	1.1361	41.77	41.75	—	—
β -Butoxyethyl.....	88	70	0.4	1.4332	1.0177	48.58	48.59	—	—

^a Wood, Such, and Scarf (2) obtained a 50% yield of *n*-octyl lactate and reported: b.p. 137° (11 mm.); d_4^{20} , 0.9304

^b These data were taken from Reference 29.

Division of Allied Chemical and Dye Company for cyclohexyl and methylcyclohexyl lactates.

EXPERIMENTAL

Lactates. β -Ethoxyethyl, β -butoxyethyl, β -chloroethoxyethyl, and tetrahydrofurfuryl lactates were prepared by a previously described method (3, 29). The last compound was also prepared in 94% yield by the alcoholysis of methyl lactate. A mixture of methyl lactate and tetrahydrofurfuryl alcohol (four moles of alcohol to one of methyl lactate; no catalyst was added) was refluxed under a column, through which methanol was removed as rapidly as it was formed. When the reaction ceased, the product (Table IV) was fractionated in vacuum. Similarly, butoxyethyl lactate (Table IV) was prepared by alcoholysis of methyl lactate, aluminum isopropoxide being used as catalyst.

3-Buten-2-yl and *n*-octyl lactates (Table IV) were prepared by the direct esterification of edible-grade lactic acid (82% concentration), sulfuric or toluene sulfonic acid being used as catalyst and benzene as an entraining agent. Five times the theoretical amount of alcohol was used for the 3-buten-2-yl ester, resulting in a yield of 77%. Twice the theoretical amount of octanol produced a yield of 52% of lactate. Purification of octyl lactate was difficult because of the presence of lactide. The latter appeared to be formed when the lactate was distilled, and since its boiling point is near that of octyl lactate, the two distilled together. The difficulty was minimized but not eliminated by distilling under low pressure and at a rapid rate. The addition of an alkaline buffer salt such as sodium acetate also helped to stabilize the lactate.

Chloroethoxyethyl lactate (Table IV) was prepared in 90% yield by the alcoholysis of methyl lactate, no catalyst being used. This ester has also been prepared by direct esterification, without catalyst, with a yield of 96% (29).

Reaction of chloroformates with hydroxy esters. The hydroxy ester (1.0 equivalent) and pyridine (1.1 eq.) were placed in a flask fitted with stirrer and dropping-funnel. The chloroformate (1.1 eq.) was added slowly, the temperature of the mixture being kept below

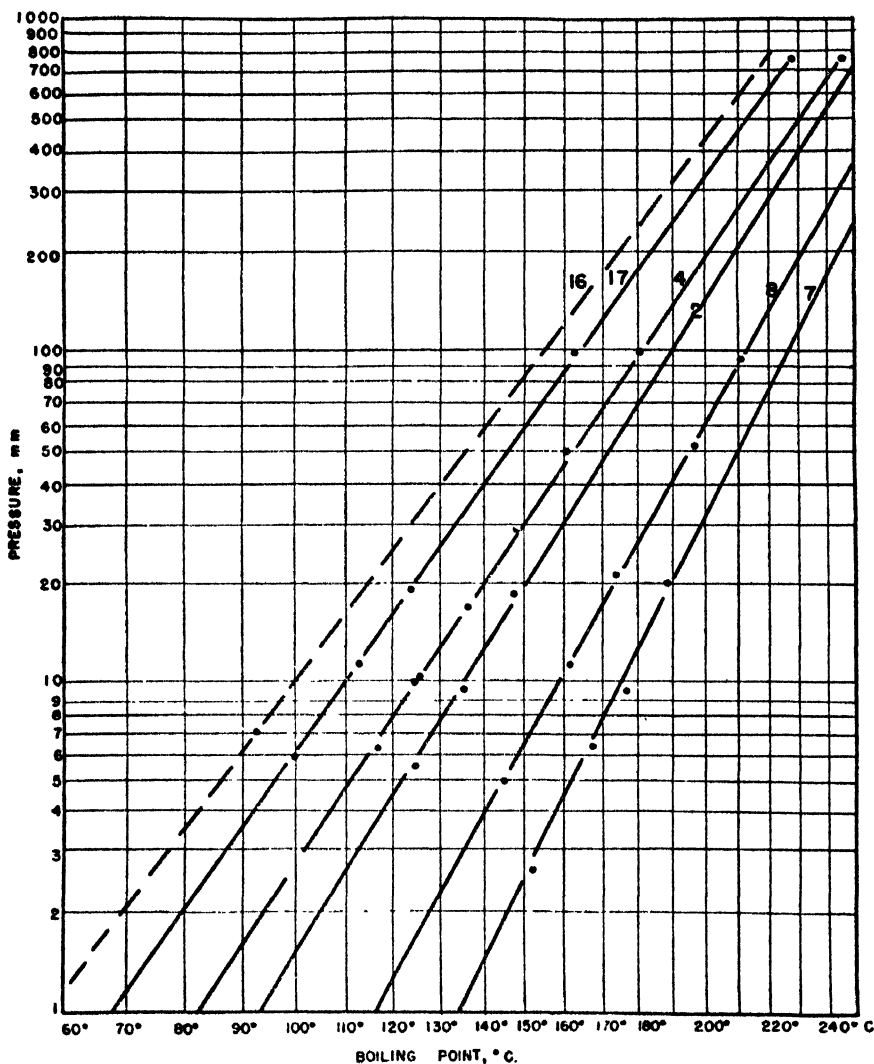


FIG. 5. BOILING POINTS OF CARBONATES (COMPOUNDS ARE NUMBERED AS IN TABLE I)

15°. After mixing of the reagents was complete, the flask was left overnight at room temperature and was then heated at about 80° for 2 hours. The product was cooled, washed several times with water, once with dilute acid to remove traces of pyridine, again with water, and then dried and distilled under reduced pressure. Relatively low yields were obtained in the acylation of the alkyl α -hydroxyisobutyrate (Table I).

Although the carbonates were prepared as described in the preceding paragraph, more recent experiments indicate that a temperature of about -10° to $+10^{\circ}$ during addition of

the chloroformate and omission of the subsequent heating lead to higher yields. It also seems preferable to filter out the pyridine hydrochloride before washing and to treat the residue and the filtrate separately. The use of dry ether as a reaction solvent also seems advantageous.

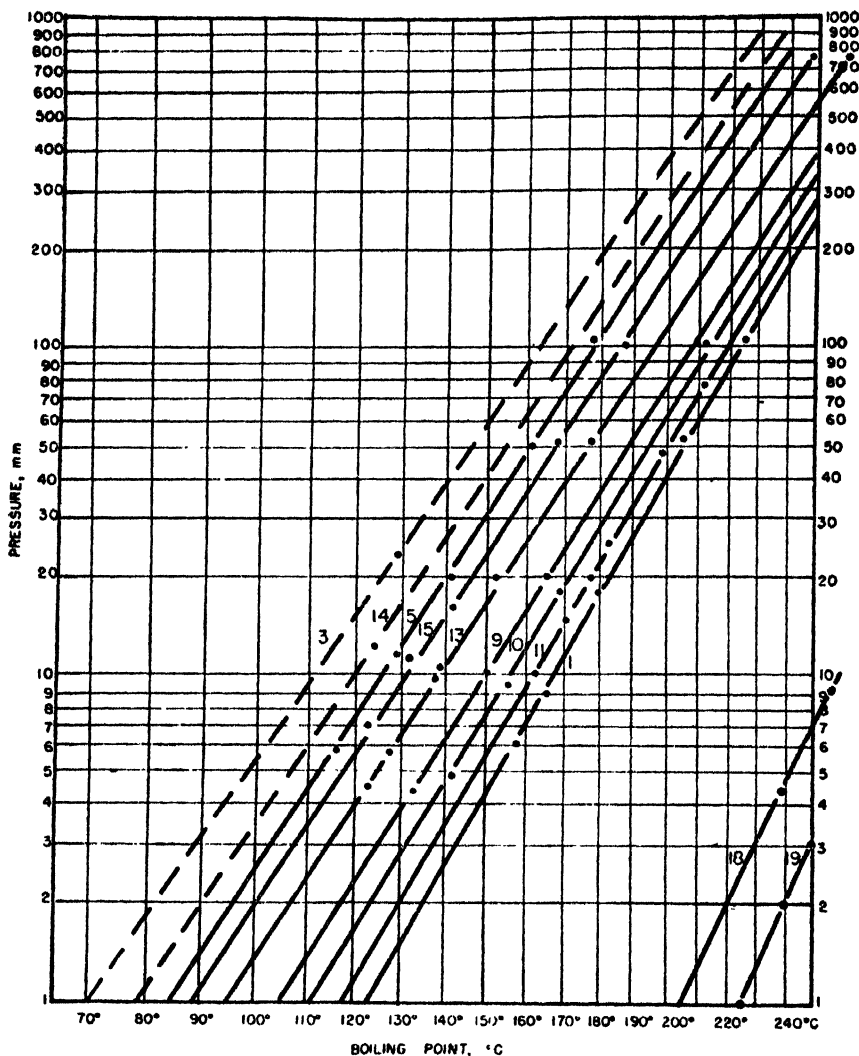


FIG. 6. BOILING POINTS OF CARBONATES (COMPOUNDS ARE NUMBERED AS IN TABLE I)

Polymerization of unsaturated esters. The esters produced by the reaction of allyl chloroformate with allyl and 3-buten-2-yl lactates readily polymerized when 1% of benzoyl peroxide was added and the monomers, in sealed tubes, were left overnight in an oven at 80°. The polymers were hardened by baking for another 24 hours at 100° and were then clear, colorless, bubble-free, insoluble, and infusible.

Boiling points. The esters were distilled under various pressures, and the boiling points thus observed were used in constructing Figures 5 and 6. The boiling points at 10 mm. pressure recorded in Table III were taken from Figures 5 and 6. The supply of esters No.

3, 14, and 16 was exhausted before other boiling points were determined, so that only one point for each is shown on Figures 5 and 6. In order to estimate their boiling points at other pressures, tentative lines were drawn through these single points; the slopes of these tentative lines were estimated from those of the adjacent lines. Esters No. 2, 6, and 12 are represented by a single line in Figure 5. The points shown are for No. 2, but those for No. 6 and 12, in the same pressure range, fell approximately on the same line.

Most of the esters began to decompose slowly when heated to 220° to 260°, and only a few boiling points at atmospheric pressure could be determined. In addition to those shown in Figures 5 and 6, ester No. 3 boiled at 220°, with considerable decomposition and polymerization. Hydroquinone was added to No. 4, after which it could be distilled (b.p. 247°) with little decomposition and no polymerization.

Cox charts (30, 31) and semi-log paper (32) have been used previously for plotting boiling points as a function of pressure. Recently described methods (26, 35) were used to estimate normal boiling points from those observed at 10 mm. (Table III).

Figure 1, prepared with data taken from references 1, 8, and 9, and Figure 2 are based on the existence of linear or approximately linear relationships between the boiling points of CH_3COOR and those of the corresponding acetoxypropionates [$\text{CH}_3\text{COOCH}(\text{CH}_3)\text{COOR}$] and ethyl carbonates ($\text{CH}_3\text{CH}_2\text{OCOOR}$). The authors, who have observed that similar relationships exist between acetates and various other esters (such as butyrates, octanoates, and benzoates), believe that figures such as 1 and 2 should be generally useful for predicting boiling points of unknown esters and checking the accuracy of determined boiling points. Figure 2 may be used to estimate the boiling point of an ethyl carbonate ($\text{CH}_3\text{CH}_2\text{OCOOR}'$) if the boiling point of the acetate ($\text{CH}_3\text{COOR}'$) is known. For the carbonates considered herein, R' is $-\text{CH}(\text{CH}_3)\text{COOR}$, and the acetate is $\text{CH}_3\text{COOCH}(\text{CH}_3)\text{COOR}$. The boiling point of this acetate (acetoxypropionate) may be estimated from Figure 1 if the boiling point of the simple acetic ester CH_3COOR is known. The latter can usually be found in the literature.

The boiling points of the carbonates used in the construction of Figures 2, 3, and 4 were taken from references 23, 33, 34, 36, and 37 or from the present work.

SUMMARY

Various carbalkoxyalkyl carbonates were prepared by acylating esters of lactic acid, glycolic acid, and α -hydroxyisobutyric acid with several chloroformates. Lactic esters (methyl, octyl, allyl, 3-buten-2-yl, β -ethoxyethyl, β -chloroethoxyethyl, β -butoxyethyl, cyclohexyl, methylecyclohexyl, and tetrahydrofurfuryl) were used in most of the preparations. The acylating agents included ethyl, butyl, amyl, β -chloroethyl, allyl, and diethylene glycol chloroformates.

Carbonates having two olefinic linkages were made by treating allyl and 3-buten-2-yl lactates with allyl chloroformate. These two unsaturated carbonates polymerized readily when heated in the presence of benzoyl peroxide. The polymers were hard, colorless, insoluble and infusible.

Several of the carbonates, which were compatible with cellulose derivatives and vinyl resins and had relatively low vapor pressures, are potentially useful as plasticizers.

PHILADELPHIA 18, PA.

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THE PREPARATION OF METHYL, ETHYL, PROPYL, AND BUTYL ORTHOCARBONATES¹

HOWARD TIECKELMANN AND HOWARD W. POST

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INTRODUCTION

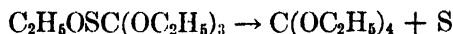
The primary purpose of this investigation was to prepare certain esters of orthocarbonic acid for use in a projected study of their chemical reactions.

Interaction of carbon tetrachloride and sodium ethoxide does not form ethyl orthocarbonate, as many other investigators have testified (2, 8, 9, 10). Chloropicrin, however, is an excellent substitute for carbon tetrachloride (1, 2, 3, 4, 6, 7).

In 1937, Connolly and Dyson (5) prepared ethyl orthocarbonate in 40% yield by the action of sodium ethoxide on thiocarbonyl perchloride, Cl_3CSCl .

PREPARATION OF THE ESTERS

Most of the orthocarbonates used in later work in this laboratory were prepared in accordance with the method of Connolly and Dyson (5). The reaction was unique but the yields were good. It was noted that, after removal of the ester layer from the reaction mixture and acidification of the aqueous residue with dilute hydrochloric acid, hydrogen sulfide was evolved and sulfur was precipitated. This fact seemed to indicate the presence of a polysulfide, presumably of sodium, in the mixture after the reaction had been completed. In order to obtain further evidence on this point, sodium ethoxide was refluxed with sulfur whereupon a coffee colored solution was formed similar to that obtained after interaction of sodium ethoxide and thiocarbonyl perchloride. This solution also evolved hydrogen sulfide and precipitated free sulfur on treatment with dilute hydrochloric acid. The reactions concerned in this synthesis can therefore be represented as follows:



Neither $\text{C}_2\text{H}_5\text{OSCCl}_3$ nor $\text{C}_2\text{H}_5\text{OSC}(\text{OC}_2\text{H}_5)_3$ was isolated in the course of this work, but the presence of the former had been demonstrated by Connolly and Dyson (5). As will be seen from Table I, the use of thiocarbonyl perchloride proved much more satisfactory than chloropicrin. Methyl, ethyl, propyl, and butyl orthocarbonates have here been prepared by this method. Only ethyl

¹ A portion of the thesis submitted by the first author in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Buffalo.

and i-butyl orthocarbonates had been prepared previously by others (5) using the thiocarbonyl perchloride reaction. Several attempts to prepare i-propyl orthocarbonate were made but these were unsuccessful.

TABLE I
PER CENT YIELDS OF ORTHOCARBONATES

ESTER	A(3)	B(4)	C(5)	D(6)	E(7)	F	G
CH ₃		60			97	48	71
C ₂ H ₅	30		40	41	80	57	78
C ₃ H ₇						49	70
C ₄ H ₉					46	39	66

F this work, Cl₃CNO₂

G this work, Cl₃CSCl

EXPERIMENTAL PART

Thiocarbonyl perchloride, Cl₃CSCl, was prepared by the method of Connolly and Dyson (5), Rathke (11), and Dyson (12). The authors are indebted to Mr. John Barone for much of the experimental work in this connection.

Methyl orthocarbonate from chloropierin. Using the method described below for the ethyl homolog, 50 g. of chloropierin (0.3 mole) and 35 g. of sodium (1.5 mole) in dry methyl alcohol gave 19.5 g. of methyl orthocarbonate, yield 48%. Physical constants: b.p. 113.5°, literature 114° (4); n_D^{20} 1.3858, literature n_D^{18} 1.3864 (4); d_4^{20} 1.020, literature $d_{18.5}^{18.5}$ 1.0232 (4).

Methyl orthocarbonate from thiocarbonyl perchloride. Using the method described below for the ethyl homolog, 56 g. (0.3 mole) of thiocarbonyl perchloride gave 29 g. of methyl orthocarbonate, yield 71%. Physical properties agreed with the product prepared from chloropierin.

Ethyl orthocarbonate from chloropierin. Ethyl alcohol, 95%, was refluxed with calcium oxide, then distilled and treated with magnesium ethoxide. The distillate from this treatment was used for the preparation of sodium ethoxide. Thirty-five grams (1.5 gr. atom) of sodium was added in small portions to about one liter of absolute alcohol. In this and in all previous steps, the system was protected from atmospheric moisture by calcium chloride tubes. The sodium ethoxide solution was warmed to 40–50° on the water-bath. The water-bath was then removed and 50 g. (0.3 mole) of chloropierin was added at such a rate that the temperature of the reaction mixture remained at about 40° to 45°. Higher temperatures resulted in lower yields. Lower temperatures than 40° resulted in the accumulation of unreacted chloropierin to a point where a sudden reaction took place with explosive violence. The addition of the chloropierin took about one hour, at the end of which the solution was thick and light yellow in color. The precipitate was sodium chloride and sodium nitrite. At this point the mixture was allowed to stand overnight.

Alcohol was distilled off from the water-bath to avoid excessive overheating. The residue was taken up with water and extracted with ether. The ether extracts were combined and fractionated; yields 31 to 35 grams, b.p. 158–160°. Less stringent precautions in connection with the exclusion of moisture during the reaction resulted in the presence of varying amounts of diethyl carbonate with the product.

Ethyl orthocarbonate from thiocarbonyl perchloride. Details here were much the same as in the preceding method. The solution of sodium ethoxide was kept in an ice-bath during addition of thiocarbonyl perchloride (56 g. in 50 cc. of dry ether) to prevent the temperature from rising above room temperature during the reaction. The system was allowed to stand overnight. Alcohol was distilled off through a column as before and the residue

extracted with water and ether. From the ether layer a fraction was isolated, b.p. 158–160°, ethyl orthocarbonate, yield 77%.

It was necessary to keep the system cool during addition of the halogen compound since otherwise the sulfur formed would react with sodium ethoxide and lower the yield considerably. The final color of the mixture was a light yellow. Interaction of sulfur and sodium ethoxide at higher temperatures produced a dark coffee color.

Propyl orthocarbonate from chloropicrin. With the method used for the ethyl compound, 50 g. of chloropicrin (0.3 mole) gave 37.1 g. of propyl orthocarbonate, yield 49%. Physical properties: b.p. 224°, literature 224.2° (3); n_D^{20} 1.4100; d_4^{20} 0.897, literature (8°) 0.911 (3).

Propyl orthocarbonate from thiocarbonyl perchloride. Using the same method as for the ethyl homolog, 56 g. (0.3 mole) of thiocarbonyl perchloride gave 53 g. of propyl orthocarbonate, 70% yield with physical properties in agreement with the above.

Butyl orthocarbonate from chloropicrin. In similar manner, 50 g. (0.3 mole) of chloropicrin gave 36.5 g. of butyl orthocarbonate, 39% yield. Physical properties, b.p. 273°; n_D^{20} 1.4216; d_4^{20} 0.8879.

Butyl orthocarbonate from thiocarbonyl perchloride. As before, 56 g. (0.3 mole) of thiocarbonyl perchloride gave 61.5 g. of butyl orthocarbonate, yield 66%. Physical properties agreed with the above.

SUMMARY

1. The preparation of methyl, ethyl, propyl, and butyl orthocarbonates by the action of the proper sodium alkoxide on chloropicrin has been repeated and data are presented on yields.

2. It has been shown that better yields may be obtained on substituting thiocarbonyl perchloride in the above syntheses.

BUFFALO, N. Y.

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THE ACTION OF ANILINE AND ITS HYDROCHLORIDE
ON CERTAIN ORTHOCARBONATES¹

HOWARD TIECKELMANN AND HOWARD W. POST

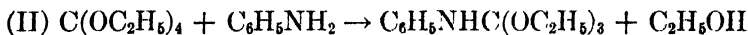
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INTRODUCTION

In 1866, Hofmann (1) found that aqueous ammonia and ethyl orthocarbonate reacted to form guanidine. Later, Bender (2) reported that aniline and ethyl orthocarbonate formed carbanilide when heated in a sealed tube. It was the purpose of this investigation to trace the steps in the formation of carbanilide from the orthocarbonate and aniline, and to follow up possible side-reactions.

DISCUSSION

In the preliminary experiments in this laboratory, ethyl orthocarbonate was refluxed with aniline for several hours. Carbanilide and triphenylguanidine were both isolated. It was later found that small amounts of aniline hydrochloride acted as a catalyst for the formation of the latter compound. For the purpose of isolating any possible intermediates, aniline and ethyl orthocarbonate were refluxed in 1:1 molar ratio under an efficient fractionating column. The progress of the reaction was noted by collecting the ethyl alcohol as formed and the reaction was stopped when an amount of ethyl alcohol had been collected which indicated reaction in a 1:1 molar ratio:



However, fractionation of the residue at reduced pressure gave a compound which was later identified as diethyl phenylimidocarbonate. Evidently the reaction had gone farther:



Experiments were then carried out to determine whether or not aniline hydrochloride could act as a catalyst for the formation of this intermediate or for any other step. First, aniline hydrochloride was refluxed with ethyl orthocarbonate for forty five minutes (reaction 6, Table I). At the end of this time the reaction appeared to have gone to completion:



Ethyl chloride was isolated in a salt and ice trap but was not identified beyond the determination of its boiling point (11–15°). A small amount of diethyl phenylimidocarbonate was also isolated here. Using butyl orthocarbonate, the yield of butyl chloride amounted to 79%, of butyl alcohol 79%, and of butyl

¹ A portion of the thesis submitted by the first author in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Buffalo.

N-phenylcarbamate 37%. By reference to reactions 1 through 5 of Table I, it will be seen that relatively small amounts of aniline hydrochloride seem to catalyze the formation of diethyl phenylimidocarbonate, while stoichiometric amounts set up a reaction in an entirely different direction, as shown in equation III.

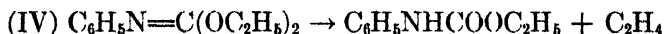
The temperature was maintained at a value sufficient to cause continued gentle refluxing. It is obvious however that continued refluxing was detrimental to the yield of diethyl phenylimidocarbonate—as a matter of fact this compound has been shown definitely to undergo pyrolysis at the temperatures used.

Smith (3) has found that dimethyl phenylimidocarbonate reacts with aniline in the cold to form carbanilide. More information relative to this reaction

TABLE I
VARIATION OF YIELDS WITH AMOUNT OF ANILINE HYDROCHLORIDE

REACTANTS, GRAMS				TIME, HRS.	YIELD, GRAMS	
No.	C ₆ H ₅ NH ₂	C(OC ₂ H ₅) ₄	C ₆ H ₅ NH ₂ Cl		C ₂ H ₅ OH	C ₆ H ₅ N=C(OC ₂ H ₅) ₂
1	12.1	25	0.0	12	9.0	6.0, 24%
2	12.1	25	0.0	5	6.0	11.7, 47%
3	11.7	25	0.5	2	11.0	18.0, 72%
4	11.7	25	0.5	1	11.0	18.0, 72%
5	11.3	25	1.0	0.25	10.0	15.5, 62%
6	0.0	25	16.8	0.75	10.5	2.5, 10%

seemed desirable. It has been found in this work that diethyl phenylimidocarbonate undergoes pyrolysis when heated to 240–260° giving phenylurethan and ethylene:

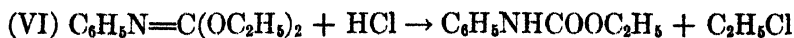


In later experiments small amounts of phenyl isocyanate and ethyl alcohol were also isolated, perhaps according to the equation:

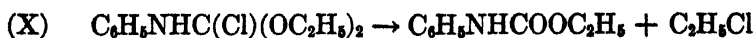
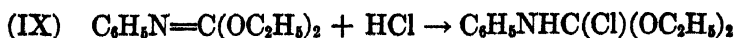
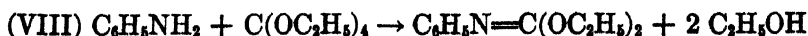
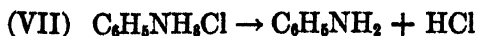


The urethan is undoubtedly the intermediate as has already been noted (4). It is proposed that decomposition takes place in accordance with equations IV and V, and not along the lines suggested for diphenyl phenylimidocarbonate by Harley-Mason (5). Ethyl N-ethylphenylcarbamate would have been an intermediate if Harley-Mason's mechanism had been followed. This compound was not detected at any time.

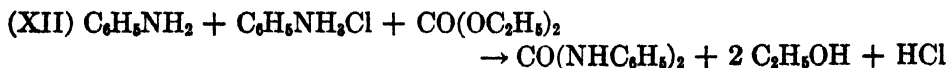
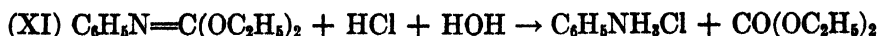
It is possible that hydrochloric acid could have been eliminated from aniline hydrochloride, and could then have added to and reacted with diethyl phenylimidocarbonate to form phenylurethan. It has been found here that dry hydrogen chloride is absorbed by diethyl phenylimidocarbonate exothermally with production of phenylurethan and probably of ethyl chloride:



On the basis of this evidence the mechanism for the formation of phenylurethan could be constructed as:



No reaction has been found in this work between pure aniline and pure diethyl phenylimidocarbonate at room temperatures. Smith (3) found carbanilide resulting from the action of dimethyl phenylimidocarbonate and aniline. Smith's results have been verified, only on addition of hydrochloric acid:



It has also been found that refluxing the mixture of aniline and diethyl phenylimidocarbonate produces carbanilide and diphenylguanidine. Inasmuch as diethyl phenylimidocarbonate decomposes pyrolytically into phenylurethan and phenyl isocyanate, this fact may also account for the formation of carbanilide:

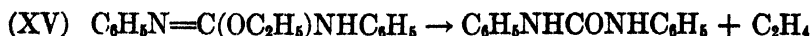
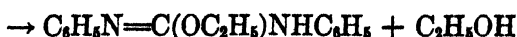


Wilm and Wischin (6) have found that equation (XIII) is valid when the reactants are heated in a sealed tube.

Lakra and Dains (7) and Schiff (8) have also submitted evidence to this end.

Thus there is no evidence of a reaction between aniline and diethyl phenylimidocarbonate at room temperatures, but if the system is heated to the temperature at which the latter decomposes according to Equation IV, triphenylguanidine results. Two mechanisms may be suggested, (A) the stepwise substitution of anilino groups for ethoxyl to form triphenylguanidine and (B) the pyrolytic decomposition of the imino compound giving phenylurethan, followed by a reaction between the urethan and aniline.

Mechanism A



Mechanism B

Begins with Equation IV

Equation XVIII has been shown to be correct by Barr (9). Further contributions were made at various times by Dains (10), and by Weith (11).

It seems logical to assume that the reaction between ethyl orthocarbonate and aniline to form the products discussed takes the course indicated by Equations I, II, IV, and XVII in that order.

EXPERIMENTAL PART

Chloropicrin and phenyliminodichloromethane were purchased from the Eastman Kodak Co. and were used after satisfactory determination of physical constants.

Aniline was purchased from the J. T. Baker Co., dried over sodium hydroxide and freshly distilled before each experiment.

Ethyl orthocarbonate and other reagents were prepared as outlined by Tieckelmann and Post (12).

Ethyl orthocarbonate and aniline. Twenty grams (0.1 mole) of ethyl orthocarbonate and 29 g. (0.31 mole) of aniline were heated on an oil-bath to reflux temperatures. At the outset the temperature of the bath was 170° but was gradually raised to 240° at the end of 12 hours. The yield of ethyl alcohol distilling smoothly throughout the reaction amounted to 13 g. (0.28 mole) at the end of the 12 hours, or 68% of the ethoxyl originally present. The residue was dissolved in hot ethyl alcohol and poured into one liter of cold dilute HCl to separate more basic material from the carbanilide. The latter was filtered and washed with water, 29 g., 84% yield. After recrystallization from glacial acetic acid, it melted at 238–239°. N, 13.0 found; 13.2, calculated. On neutralization of the acid filtrate with NH₄OH, 0.8 g. of *sym.*-triphenylguanidine precipitated, m.p. 144–145°, N, 14.5 found; 14.63, calculated, no depression in mixed melting point with sample purchased from Eastman Kodak Company.

Twenty-five grams (0.13 mole) of ethyl orthocarbonate and 12.1 g. of aniline (0.13 mole) were refluxed similarly for 10 hours. Products were 8 g. of ethyl alcohol, 6 g. of a liquid boiling at 126° (12 mm.) and 9 g. of unreacted material. The solid which formed and clogged the fractionating column proved to be carbanilide, m.p. 239°. The liquid distillate was diethyl phenylimidocarbonate, b.p. 247° (751 mm.), n_D^{20} 1.5161.

Anal. Calc'd for C₁₁H₁₅NO₂: C, 68.36; H, 8.85; N, 7.25; C₂H₅O, 46.6.

Found: C, 68.9; H, 8.3; N, 7.33; C₂H₅O, 45.2.

Ethyl orthocarbonate and aniline in the presence of aniline hydrochloride. Twenty grams (0.1 mole) of ethyl orthocarbonate, 29 g. (0.31 mole) of aniline, and 0.5 g. (0.04 mole) of aniline hydrochloride were refluxed at temperatures slowly rising to 250° with constant distillation of ethyl alcohol. After 10 hours, 10 g. (0.22 mole) of alcohol had been removed after which 11 g. (0.12 mole) of unreacted aniline distilled over. A hot alcoholic extract of the solid residue was poured into one liter of ice cold dilute hydrochloric acid and the insoluble diphenylcarbanilide filtered and washed with water. Yield 17.5 grams (64%), m.p. 238–239° after recrystallization from glacial acetic acid, nitrogen found 13.2, calculated 13.20. *Sym.*-triphenylguanidine was precipitated from the acid liquors by addition of ammonium hydroxide. It was washed with alcohol and recrystallized therefrom, m.p. 145–146°.

Anal. Calc'd for C₁₉H₁₇N₃: C, 79.46; H, 5.97; N, 14.63.

Found: C, 79.7; H, 6.06; N, 14.4.

Using ethyl orthocarbonate and aniline in 1:1 molar ratio and distilling the residue at reduced pressure, the main product was diethyl phenylimidocarbonate b.p. 123–125° (12 mm.), nitrogen, found 7.21; calculated, 7.25. Data on comparative yields will be found in Table I.

Ethyl orthocarbonate and aniline hydrochloride were allowed to react in 1:1 molar ratio, 0.13 mole of each, under reflux conditions, with the temperature slowly rising to 100° over a period of fifteen minutes. After an additional hour's refluxing, 10.5 g. of ethyl alcohol was distilled and five grams of ethyl orthocarbonate was recovered. The residue was distilled at reduced pressure between 124° and 145° at 12 mm., weight 18.2 g. On further fractionation, there was obtained 2.5 g. of diethyl phenylimidocarbonate, b.p. 124–126° (12 mm.) and 12 g. of phenylurethan, m.p. 49–50°, nitrogen, found 8.58, calculated, 8.49. The volatile product of the reaction, collected in an ice and salt trap was undoubtedly ethyl chloride although actual identification was incomplete.

Butyl orthocarbonate and aniline hydrochloride were refluxed as above, using 0.033 mole of each. A product, assumed to be butyl chloride was collected, weight 2 g., b.p. 76–78°, n_D^{20} 1.4030, yield 66%. This product gave a negative halogen test with alcoholic silver nitrate but after fusion with sodium and extraction with water, easily precipitated silver chloride. The residue, 3.5 g., when recrystallized from ligroin gave butyl N-phenylcarbamate, m.p. 58–60°, nitrogen, found 7.39; calculated, 7.26.

Thermal decomposition of diethyl phenylimidocarbonate. These decomposition reactions were run in a 200-cc. flask connected with a fractionating column. The column was connected directly with a trap immersed in ice-water. Two 1" x 10" test tubes, each containing 18 g. of bromine covered with a little water were connected in series with this trap. The exit tube from the second bromine reaction tube was connected to a funnel inverted over a saturated solution of sodium bisulfite. Thirty grams of freshly distilled diethyl phenylimidocarbonate was placed in the flask, then heated to 260°. A gas was given off and absorbed by the bromine. At the end of two hours, when the evolution of gas had ceased, the contents of the bromine tubes were decolorized with sodium bisulfite, washed with sodium bicarbonate and water, dried over calcium chloride and distilled. Yield of ethylene dibromide 23 g., 79% b.p. 130° (uncorr.), m.p. 9°, n_D^{20} 1.5372. The residue in the flask was distilled at reduced pressures, and gave a small amount of phenyl isocyanate and 18 g. of phenylurethan, m.p. 50–51°, nitrogen, found 8.62; calculated, 8.49. A small amount of what may have been carbanilide, m.p. 235° had sublimed on the cold-finger condenser and from the residue in the reaction flask there was obtained a small amount of what may have been triphenyl cyanurate, m.p. 262–265°, literature 270°.

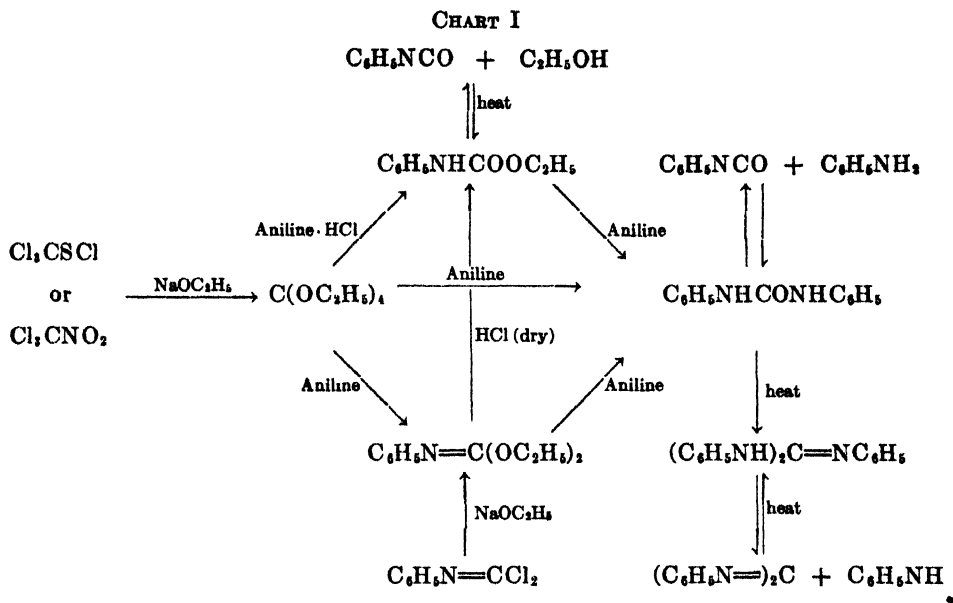
Diethyl phenylimidocarbonate and aniline. Equimolar parts (0.078 mole each) of diethyl phenylimidocarbonate and aniline were refluxed. The outlet of the condenser was provided with two bromine tubes as before. The oil-bath with which the system was heated was kept at 230° for 45 minutes with no evidence of the evolution of ethylene. But at 250° ethylene was produced and was absorbed by the bromine. At the end of two hours the evolution of ethylene had ceased. Ethylene bromide 9.3 g., 63% yield. Ethyl alcohol, 3.2 g., 80% yield was obtained by partially distilling the residue. The solid remaining was recrystallized from glacial acetic acid, weight 4 g., 24% yield, of carbanilide, m.p. 238–239°, nitrogen, 13.1 found; 13.20, calculated. There was also obtained 7.5 g. of *sym.*-triphenylguanidine, 34% yield, m.p. 144–145°, nitrogen, found 14.5; calculated, 14.63. Equimolar parts of these two reactants (0.086 mole) were mixed and allowed to stand at room temperature. There was no visible sign of change at the end of one month. Periodically, 1 cc. of this mixture was removed and treated with 20 cc. of 3 N hydrochloric acid. Both carbanilide and phenylurethan are insoluble under these conditions. An odor of ethyl carbonate was easily detected in each test. One drop of concentrated hydrochloric acid was added to 1 cc. of the above mixture of aniline and diethyl phenylimidocarbonate. At the end of 24 hours a thick precipitate had formed, which on filtration and recrystallization from glacial acetic acid gave about 0.6 g. of carbanilide, m.p. 235°. A mixed m.p. with a known sample of carbanilide showed no depression. A small amount of phenylurethan was isolated

when the filtrate was poured into water, m.p. 50–51°. The mixed melting point again was identical.

Dry hydrogen chloride and diethyl phenylimidocarbonate. Twenty grams (0.1 mole) of diethyl phenylimidocarbonate was placed in a 250-cc. flask and dry hydrogen chloride gas passed over the liquid surface. The gas was absorbed exothermally, with rise of temperature to 40°. Excess hydrogen chloride and possibly other volatile products were removed by suction and from the residue there was obtained by filtration 17.2 g. of a solid, 17.1 theoretical for phenylurethan, m.p. 50–51° (after recrystallization from ethyl alcohol) no depression on determination of mixed melting point with a known sample.

SUMMARY

1. Aniline reacts with ethyl orthocarbonate to form carbanilide, diethyl phenylimidocarbonate and triphenylguanidine (Chart I).



2. Aniline hydrochloride reacts with ethyl orthocarbonate to form phenylurethan (Equation III).

3. Diethyl phenylimidocarbonate decomposes when heated to form phenylurethan and ethylene (Equation IV).

4. Dry hydrogen chloride reacts with diethyl phenylimidocarbonate to form phenylurethan (Equation VI).

5. Diethyl phenylimidocarbonate does not react with aniline in the cold. Carbanilide and phenylurethan are formed in the presence of hydrochloric acid (Equations XI, XII).

6. Pure dry diethyl phenylimidocarbonate reacts with aniline to form carbanilide at 250–260° (Equations IV, XVII).

BUFFALO, N. Y.

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STUDIES IN SILICO-ORGANIC COMPOUNDS. V. THE PREPARATION AND PROPERTIES OF CERTAIN POLYETHERS FROM TETRACHLOROSILANE, HEXACHLORODISILANE, AND HEXACHLORODISILOXANE¹

EDWIN W. ABRAHAMSON, IRVING JOFFE, AND HOWARD W. POST

Received November 6, 1947

INTRODUCTION

The purposes of this investigation were twofold. It was desired to determine the general physical properties of silicon polyethers of large organic radicals, and to prepare certain polyethers of tetrachlorosilane, hexachlorodisilane, and hexachlorodisiloxane for comparison of their properties with compounds obtained in another section of the work (1).

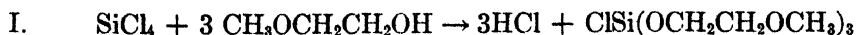
Von Ebelman (2) synthesized tetraethoxysilane and tetra-*i*-amoxysilane by treating the anhydrous alcohol with tetrachlorosilane. In 1863, Friedel and Crafts (3) entered the field, using the method of von Ebelman and preparing a mixed polyether, amoxytriethoxysilane, by the successive action of ethyl and amyl alcohols. Two years later these same investigators (4) prepared tetramethoxysilane, isolating in addition a high-boiling product, hexamethoxydisiloxane. A complete bibliography on the subject would include references dated almost to the present time (5, 6).

However, polyethers can sometimes more conveniently be prepared from other polyethers of silicon, preferably those with smaller organic radicals. Thus Friedel and Crafts (3) in 1863 treated tetraethoxysilane with methyl alcohol, obtaining dimethoxydiethoxysilane. Later, Herthorn (7) allowed ethyl alcohol to react with tetraphenoxysilane, obtaining almost quantitative conversion to tetraethoxysilane and phenol. Other work followed (6, 8).

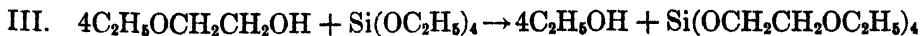
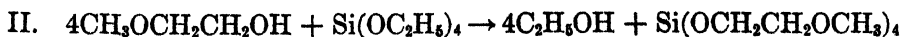
DISCUSSION

In this work, tetrabutoxysilane has been prepared once more, by the action of anhydrous butyl alcohol on tetrachlorosilane. No difficulties were met with.

Methyl Cellosolve was allowed to react with tetrachlorosilane in the molar ratio of 5:1 but even in this proportion, one chlorine atom remained attached to silicon:



The preparation of the tetraethers however was brought about much more satisfactorily by radical interchange between the higher alcohol and a lower tetraether:



¹ A portion of the work on which this paper is based was made possible by a contract with the Office of Naval Research.

These processes presented no especial difficulties and will be described more fully under Experimental Part. The physical properties of the three compounds thus prepared are given in Table I.

Tri- β -methoxyethoxysilane was most susceptible to hydrolysis. This was to be expected, since there remained one chlorine attached to silicon. Although tetra- β -methoxyethoxysilane was somewhat miscible with water, it did not hydrolyze immediately on solution. However, on long standing a gel was

TABLE I
PHYSICAL PROPERTIES

	B.P. °C/MM.	n_D	d	VISCOSITY, POISE
$\text{Si}(\text{OC}_2\text{H}_5)_4$		1.3825(obs.) ^a 1.3821(8.9) ^b		
$\text{ClSi}(\text{OCH}_2\text{CH}_2\text{OCH}_3)_3$	289/740 186/9	1.4220 ^c	1.0804 ^e 1.0756 ^f	0.0352 ^g .0316 ^h
$\text{Si}(\text{OCH}_2\text{CH}_2\text{OCH}_3)_4$	292/740 183/9	1.4213 ^b	1.0781 ^e 1.0680 ^f	.0362 ^g .0288 ^h
$\text{Si}(\text{OCH}_2\text{CH}_2\text{OC}_2\text{H}_5)_4$	312/740 200/9	1.4226 ^d	1.0184 ^e 1.0139 ^f	.0832 ^g .0334 ^h

^a 20.2°.

^b 20°.

^c 20.3°.

^d 20.5°.

^e 20°.

^f 20°.

^g 20°.

^h 25°.

Viscosities were determined by the method of Mack and France (10).

formed. In acid solution no hydrolysis was evident, but in caustic media hydrolysis was almost instantaneous. Tetra- β -ethoxyethoxysilane is immiscible in neutral, acid, and caustic media. Hydrolysis was slower than in the case of the methyl homolog described above.

Phenyl Cellosolve reacted with tetraethoxysilane to give tetra- β -phenoxyethoxysilane.

The action of anhydrous alcohols on hexachlorodisiloxane produced variable results. Ethyl alcohol, under the conditions of this work produced almost entirely tetraethoxysilane. Propyl alcohol formed hexapropoxydisiloxane in 27% yield and butyl alcohol produced a 15% yield of hexabutoxydisiloxane. Anhydrous ethyl alcohol reacted with hexachlorodisilane to give a 25% yield of hexaethoxydisilane. The yield of the corresponding propyl compound was 12%.

EXPERIMENTAL PART

Tetrabutoxysilane. Tetrachlorosilane (17 cc., 0.15 mole) was added dropwise to 65 cc., 0.70 mole, of butyl alcohol, anhydrous. After refractionation, the product boiled at 273–277° (760 mm.), d_{25}^{25} 0.913, found; d_{25}^{25} 0.899 literature (8); Si 8.91, 8.84, theoretical 8.76.

Methyl Cellosolve and Ethyl Cellosolve (ethylene glycol monomethyl and monoethyl ethers), were made available through the courtesy of Carbide and Carbon Chemicals Corp. Each of these compounds was thoroughly dried over sodium sulfate before use. Their physical properties were satisfactory.

Tri- β -methoxyethoxychlorosilane. Methyl Cellosolve was fed into freshly distilled tetrachlorosilane (150 cc. and 44 cc. respectively) at a rate of three drops per second. The Methyl Cellosolve formed a separate layer on top of the silicon compound. An endothermic reaction set in at the end of ten minutes. Hydrogen chloride was absorbed in a trap containing 50% sodium hydroxide. The reaction mixture was heated to reflux for thirty minutes to drive off the last traces of acid. Fractional distillation yielded 70 g. of product, a yield of 9% based on the tetrachlorosilane used. The product hydrolyzed readily in dilute sodium hydroxide with production of chloride ion (silver nitrate test). The molecular weight was determined by the cryoscopic method, in benzene (11) as 284, theoretical 288.7. This compound was miscible with water, but with slight turbidity indicating hydrolysis. Absolute viscosity was determined with an Ostwald viscosimeter using the method of Mack and France (10) and the formula: $n_1/n_2 = d_{1t_1}/d_{2t_2}$, where n is the viscosity in poise units, d the density and t the time of flow in seconds. The reference viscosity used in these determinations was that of water, 0.0088 at 25° and 0.0100 at 20° (10). Physical properties of this and the succeeding two products are listed in Table I.

Tetra- β -methoxyethoxysilane. The method used here was substantially the same as was used in the preparation of the chloro derivative previously described. In 5:1 molar ratio, Methyl Cellosolve and tetraethoxysilane were mixed and subjected to 8 hours reflux, followed by fractional distillation. The product weighed 152 g., 90% yield. Observed molecular weight was 327, theoretical 328.3. This compound was miscible with water but very slow of hydrolysis, save in alkalis.

Tetra- β -ethoxyethoxysilane. Using the same procedure, this compound was obtained in 94% yield, 182 g. Observed molecular weight was 387, theoretical 384.5.

Tetra- β -phenoxyethoxysilane. Phenyl Cellosolve, dried over sodium sulfate, and freshly distilled tetraethoxysilane were refluxed in a 5:1 molar ratio, 200 cc. of the Cellosolve and 70 cc. of tetraethoxysilane. After 6 hours of reflux 65 cc. of ethyl alcohol had been obtained, 92% of theoretical. The mixture became very dark. Excess Phenyl Cellosolve was distilled off whereupon the material remaining in the flask solidified. After recrystallization of the latter from benzene, 10 g. of product was obtained, probably tetra- β -phenoxyethoxysilane, a white crystalline solid m.p. 85–87°. Tetra- β -phenoxyethoxysilane is immiscible in water and sodium hydroxide. A white precipitate was formed with water and acid; Si: 4.95, 4.91, theoretical: 4.86.

Hexachlorodisiloxane and ethyl alcohol. Absolute ethyl alcohol (110 cc., 1.9 moles) was added dropwise to 80 g. (0.28 mole) of hexachlorodisiloxane. The reaction was vigorous, hence addition was slow, but as the addition of alcohol progressed, evolution of hydrogen chloride slowed down. After about one-fourth of the alcohol had been added, a layer began to form on top of the reaction mixture and despite constant shaking, this layer remained to the end. After addition, the system was refluxed at 107° from 5 to 6 hours, then the excess alcohol distilled off. The main product was tetraethoxysilane, b.p. 65–70° (18 mm.), literature 68.5° (18 mm.) (12).

Hexachlorodisiloxane and propyl alcohol. Anhydrous propyl alcohol (50 cc., 0.66 mole) was added dropwise to 20 cc. (0.07 mole) of hexachlorodisiloxane over a period of one hour. After the alcohol had been added, the mixture was heated in an oil-bath at 120° until evolu-

tion of hydrogen chloride had ceased. Excess alcohol was distilled off and the remaining liquid distilled at 25 mm. giving:

125-130°	6.0 grams	Si(OC ₃ H ₇) ₄
150-170°	6.3 grams	intermediates
205-208°	8.0 grams	(C ₃ H ₇ O) ₂ SiOSi(OC ₃ H ₇) ₂

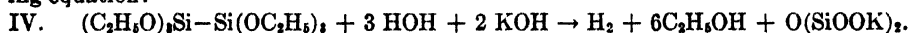
Hexapropoxydisiloxane is a colorless liquid with a rather sharp odor. It is stable in air but hydrolyzes very slowly in caustic. The yield was 22%. Literature b.p. 190° (20 mm.), 330° (760 mm.) (14), d_4^{25} 0.976 found; d_4^{25} 0.977 literature (14); Si: 13.55, 13.10, theoretical: 13.13.

Hexachlorodisiloxane and butyl alcohol. Anhydrous butyl alcohol (55 cc., 0.59 mole) was added dropwise to 25 g. (0.09 mole) of hexachlorodisiloxane. After addition, the mixture was refluxed until the evolution of hydrogen chloride had ceased. After excess alcohol had distilled off, the remaining liquid was distilled at 20 mm. with the following fractions coming over:

150-160°	7.0 grams	Si(OC ₄ H ₉) ₄
170-200°	3.7 grams	intermediates
245-250°	7.0 grams	(C ₄ H ₉ O) ₂ SiOSi(OC ₄ H ₉) ₂

Hexabutoxydisiloxane is a colorless oily liquid stable in air and water but hydrolyzing slowly in caustic. It was prepared in 15.6% yield; Si: 11.20, 10.70, theoretical: 10.95.

Hexachlorodisilane and ethyl alcohol. Absolute ethyl alcohol (120 cc., 2.1 moles) was added dropwise to 82.5 g. (0.306 mole) of hexachlorodisilane. The bulk of the reaction did not take place until the system was refluxed. By the time the temperature had reached 100°, the two separate layers which had formed on addition of the reactants, had merged. Reflux of 6 hours was, however, necessary. The first fraction to distill, after tetraethoxysilane, came over at 132-133° (18 mm.), probably hexaethoxydisilane, literature 140-150° (18 mm.) (13). The yield was 25 g. Hexaethoxydisilane (0.5653 g.), prepared as described, was allowed to react with 10 cc. of 30% potassium hydroxide at room temperature. Hydrogen was immediately evolved, exothermally, and collected by water displacement. Corrected volume of water was 36.9 cc., theoretical 38.83 cc. The reaction is expressed by the following equation:



The detailed procedure for this determination will be found in another contribution of this series (1).

Hexachlorodisilane and propyl alcohol. Anhydrous propyl alcohol (45 cc., 0.60 mole) was added dropwise to 20 cc. (0.08 mole) of hexachlorodisilane. After the alcohol had been added, the mixture was heated until no further evolution of hydrogen chloride was noticed. The excess alcohol was distilled off, and the remainder was fractionated at 25 mm. The main fractions were Si(OC₃H₇)₄, b.p. 125-130° (25 mm.), intermediate products, and hexapropoxydisilane 4 g., b.p. 190-195° (25 mm.). On treatment with 10 cc. of hot 30% sodium hydroxide, 1.030 g. of hexapropoxydisilane evolved 55.8 cc. of hydrogen (corr.), theoretical 57.5 cc.

SUMMARY

1. Tri- β -methoxyethoxychlorosilane has been prepared by the action of Methyl Cellosolve on tetrachlorosilane. Tetra- β -methoxyethoxysilane and tetra- β -ethoxyethoxysilane have been prepared by the action of Methyl Cellosolve and of Ethyl Cellosolve, respectively, on tetraethoxysilane. A product, probably tetra- β -phenoxyethoxysilane, has been obtained from the action of Phenyl Cellosolve on tetraethoxysilane. The physical properties and certain chemical properties of these compounds have been determined and reported.

2. Hexachlorodisiloxane and absolute ethyl alcohol react with evolution of hydrogen chloride. The main product, under conditions outlined, is tetra-

ethoxysilane. Larger yields of the expected hexaalkoxydisiloxanes have been obtained from the action of anhydrous propyl and butyl alcohols on hexachlorodisiloxane.

3. Hexachlorodisilane reacts with absolute ethyl alcohol and absolute propyl alcohol to form hexaethoxydisilane and hexapropoxydisilane respectively. The determination of the purity and identity of these products is materially aided by a study of their reaction with hot caustic alkali with practically quantitative evolution of hydrogen.

BUFFALO, N. Y.

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STUDIES IN SILICO-ORGANIC COMPOUNDS. VI. THE
PREPARATION AND PROPERTIES OF POLYETHERS
FROM TRICHLOROSILANE¹

MARTHA E. HAVILL, IRVING JOFFE, AND HOWARD W. POST

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INTRODUCTION

In the beginning of this work, silicon polyethers such as HSi(OR)_3 were desired, but certain properties of hydrogen connected to silicon made it advisable to spend considerable time on the preparation of compounds with hydrogen thus linked, and to study their reaction with caustic alkali. The problem opened with a preliminary study of the action of certain low-molecular-weight alcohols on trichlorosilane.

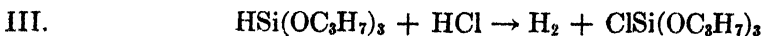
In 1867, Friedel and Ladenburg (1) prepared triethoxysilane by the treatment of trichlorosilane with anhydrous ethyl alcohol. Ruff and Albert (2) attempted the same preparation starting with trifluorosilane but obtained tetraethoxysilane instead of the expected tri ether:



Taurke (3) extended this synthesis to include higher alcohols and other investigators followed (4).

The work herein described on the preparation or attempted preparation of several trialkoxysilanes very early led to the realization that at room temperatures, in the presence of hydrochloric acid, hydrogen is lost, in fact quantitatively when the radical weights are low. Higher homologs lose this tendency somewhat. The trialkoxysilanes pass over to tetraalkoxysilanes and hexaalkoxydisiloxanes. In most cases these compounds were successfully prepared and kept without reaction at zero degrees but hydrogen evolution began with slow spontaneous warming up to room temperatures.

Thus anhydrous ethyl alcohol and trichlorosilane reacted to form tetraethoxysilane and hexaethoxydisiloxane. The result was analogous when propyl alcohol was used. Butyl alcohol formed tributoxysilane in small amounts. Most of the product even here was tetrabutoxysilane. In all of these reactions the temperature was kept below that of the room, and all access to the atmosphere was closed. The system in each case was kept closed until long after room temperatures had been reached, to capture all hydrogen which escaped. Runs were made with varying proportions of alcohol. The amount of hydrogen collected was proportional to the amount of silicon ether present. The formation of tetraalkoxysilanes might be tentatively illustrated by the following equations:



¹ The work on which this paper is based comprises a part of a program of research being carried out under contract with the Office of Naval Research.

Disiloxanes might have formed through hydrolysis. These assumptions are quite tentative; a more complete mechanism is under consideration and the laboratory investigation is being continued.

Attempts were made to remove hydrogen chloride by sweeping it out with nitrogen, but there was no increased yield of the desired trialkoxysilane when this was done. Interaction of trichlorosilane and a sodium alkoxide had no effect in this direction. The best yields of trialkoxysilanes were obtained when benzene was added to the system, as a solvent. These results are illustrated in Table I.

Thus benzene definitely exerts a stabilizing effect on the trialkoxysilanes, inhibiting the transformation to tetraalkoxysilane and hexaalkoxydisiloxanes.

TABLE I
EFFECT OF REACTION CONDITIONS ON YIELDS

1. C_2H_5OH	$Si(OC_2H_5)_4 + (C_2H_5O)_2SiOSi(OC_2H_5)_2$
2. C_2H_5OH in C_6H_6	$HSi(OC_2H_5)_3$, 45%
3. C_2H_5OH in C_6H_6 with standing..	$HSi(OC_2H_5)_3$, 28.8%
4. C_2H_7OH	$Si(OC_2H_7)_4$
5. C_2H_7OH in C_6H_6	$HSi(OC_2H_7)_3$, 53%
6. C_4H_9OH	$HSi(OC_4H_9)_3$, 16%
7. C_4H_9OH in C_6H_6	$HSi(OC_4H_9)_3$, 71%
8. <i>i</i> - C_4H_9OH in C_6H_6	$HSi(OC_4H_9)_3$, 48.5%

EXPERIMENTAL PART

Trichlorosilane and ethyl alcohol. Absolute ethyl alcohol (72 cc., 1.25 moles) was added dropwise to 25 cc. (0.25 moles) of trichlorosilane, at temperatures around 0°. After addition, the reaction mixture was slowly allowed to warm up to room temperatures, then refluxed and distilled. Approximately 15 cc. of the product boiled between 164° and 172°, probably tetraethoxysilane, while 15.7 cc. boiled between 232° and 240°. No triethoxysilane was detected. During the second later runs, apparatus was set up to catch any gas evolved, by water displacement. No evolution of gas was noticed as long as the temperature of the system was kept at 0° or thereabouts. Enough liquid product was collected from four runs to fractionate. There were isolated tetraethoxysilane, b.p. 135° (18 mm.) and hexaethoxydisiloxane, b.p. 160° (18 mm.), literature 95.5–96.5° (3–5 mm.) (6) and 235° (760 mm.) (7). The boiling point of hexaethoxydisiloxane was further checked against a sample prepared in this laboratory as described below.

Trichlorosilane and ethyl alcohol in benzene. Dry ethyl alcohol (35 cc., 0.6 mole) was added dropwise at 0° to a mixture of 0.15 mole (15 cc.) of trichlorosilane and 50 cc. of benzene. After two hours standing, and distillation of excess alcohol, there were obtained, at 760 mm., 12 g. of triethoxysilane, (45% yield) b.p. 132–135°, d_4^{25} 0.8745 and 3 g. of tetraethoxysilane, b.p. 165–170°, literature 134° (1) and 165–166° (2) respectively. Triethoxysilane hydrolyzes in water but more easily in caustic. To determine the effect of standing, the reaction was repeated with a twelve-hour interval at room temperatures between complete addition of the alcohol and distillation. Using the same amounts as above, 7 g. of triethoxysilane (28.8% yield) was obtained and 9 g. of tetraethoxysilane.

Trichlorosilane and propyl alcohol. Anhydrous propyl alcohol (50 cc., 0.66 mole) was added dropwise over a period of one hour to 17 cc. (0.17 mole) of trichlorosilane. The addition was carried out in an ice-bath and the reaction mixture was allowed to warm up to room temperature and stand overnight. Only propyl alcohol and 26 cc. of tetraethoxy-

silane were obtained, b.p. 224–225° (750 mm.), literature 225–227° (760 mm.) (5), d_4^{25} 0.9150; literature d_4^{25} 0.9158 (5). Evolution of hydrogen did not begin until the system had warmed to room temperature. Three more runs were made and the evolved hydrogen collected for quantitative determination. Description of hydrogen determinations will be found elsewhere in this paper. Use of sodium propoxide instead of propyl alcohol proved unsatisfactory. Sweeping out the apparatus with dry nitrogen did not produce better results.

Trichlorosilane and propyl alcohol in benzene. Anhydrous propyl alcohol (40 cc., 0.6 mole) was added dropwise to a solution of 15 cc. (0.15 mole) of trichlorosilane and 50 cc. of benzene. After standing for 24 hours, there were isolated 4 g. of tetrapropoxysilane and 16 g. (53% yield) of tripropoxysilane, b.p. 190–194° (750 mm.), d_4^{25} 0.882; literature d_4^{25} 0.895 (3).

Trichlorosilane and butyl alcohol. Anhydrous butyl alcohol (45 cc., 0.5 mole) was added dropwise to 15 cc. (0.15 mole) of trichlorosilane at 0°. The reaction mixture was allowed to warm up to room temperature by standing overnight, and on distillation there was obtained 6 g. of tributoxysilane (16% yield), b.p. 115–120° (13 mm.), 228–237° (760 mm.); Si: 11.10, 11.15, theoretical: 11.30, mol. wt.: 244 (cryoscopic in benzene), theoretical: 248; d_4^{25} 0.889. Tetrabutoxysilane was also obtained, 12 g., b.p. 135–146° (13 mm.).

Trichlorosilane and butyl alcohol in benzene. Anhydrous butyl alcohol (50 cc. 0.54 mole) was added dropwise to a solution of 15 cc. (0.15 mole) of trichlorosilane in 50 cc. of benzene

TABLE II
HYDROGEN DETERMINATIONS, LATER RUNS, NaOH TREATMENT

COMPOUND USED	GRAMS	H ₂ FOUND	H ₂ (CORR.)	H ₂ (THEORETICAL)	DEVIATION FROM THEORETICAL
HSi(OC ₂ H ₅) ₃	0.890	126 cc.	114 cc.	121.5 cc.	6%
HSi(OC ₃ H ₇) ₃	1.102	131 cc.	119 cc.	120.5 cc.	1%
HSi(OC ₄ H ₉) ₃	1.353	128 cc.	116 cc.	122 cc.	5%
HSi(OC ₄ H ₉) ₃	1.251	123 cc.	111 cc.	114.2 cc.	3%

at 0°. After 3 hours of standing, there were obtained 26.1 g. of tributoxysilane (71% yield), b.p. 237–238° (760 mm.), and 2.5 g. of tetrabutoxysilane, b.p. 273–277° (760 mm.). A duplicate run, after standing two days gave only 7 g. of tributoxysilane, 20% yield.

*Trichlorosilane and *i*-butyl alcohol in benzene.* *i*-Butyl alcohol (50 cc., 0.54 mole) and 10 cc. (0.10 mole) of trichlorosilane in 50 cc. of benzene, treated as above, reacted to form 11.5 g. (48.5% yield) of tri-*i*-butoxysilane, b.p. 224–228° (751 mm.), literature 240–242° (760 mm.) (3). Tetra-*i*-butoxysilane, 32 g., b.p. 255–258° (760 mm.) was also obtained; d_4^{25} 0.891; Si: 11.22, 11.45, theoretical: 11.30, mol. wt. (cryoscopic in benzene): 251, theoretical: 248.

Gas analyses. A Fisher Orsat apparatus was used. Pyrogallic acid first took out oxygen, if any, thus giving an approximation of the amount of air present. The gas was then passed through a copper oxide tube, heated to 300–325° to take out hydrogen. This was repeated several times until constant volume had been attained. The gas was then run through sodium hydroxide to ascertain the presence or absence of carbon dioxide which might have resulted from the burning of hydrocarbons. None was found.

Results in Table II were obtained by treating each sample with 10 cc. of 30% NaOH and collecting the evolved gas by water displacement. An aliquot portion of this gas was analyzed as described above. Theoretical values for hydrogen were determined from the equation: $V. 2HSi(OC_2H_5)_3 + HOH (NaOH) \rightarrow 2 H_2 + (C_2H_5O)_2SiOSi(OC_2H_5)_3$.

Silicon analyses were carried out according to a method already in the literature, (8).

SUMMARY

1. Under the conditions of these experiments, trichlorosilane and ethyl alcohol react at 0° in normal manner but when the reaction mixture is warmed to room

temperatures, secondary reactions take place by which tetraethoxysilane, hexaethoxydisiloxane, and hydrogen are formed. Propyl alcohol reacts similarly but butyl alcohol gives a 16% yield of tributoxysilane.

2. The yield of trialkoxysilane is considerably increased by the use of benzene as a solvent. The yields vary in the order $C_2H_6 < C_3H_7 < C_4H_9$. Tri-*i*-butoxysilane has also been prepared.

3. Evolution of hydrogen when a silane is treated with aqueous caustic at room temperatures has been studied and has been found to be nearly quantitative.

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CIS AND TRANS β -AROYLACRYLIC ACIDS
AND SOME DERIVATIVES¹

ROBERT E. LUTZ AND GEORGE W. SCOTT²

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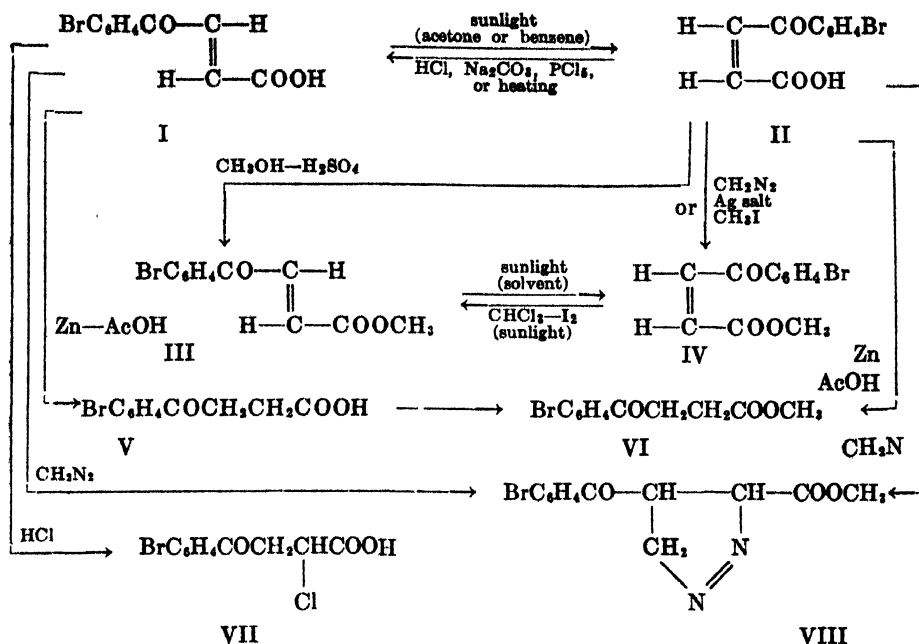
The study with respect to ring-chain tautomerism, of various α - and β -substituted β -aroylacrylic acids and their derivatives (1), and especially of the amides of *cis* and *trans* β -(4-bromobenzoyl)- α -methylacrylic acids (1g), has led to the present investigation, for comparative purposes, of the β -(4-bromobenzoyl)acrylic series (I–II). In this series, which carries no substituent on the ethylene linkage, the unsaturated system was expected to be sterically very labile and chemically reactive, and to show little if any tendency to exist or to function in cyclic forms such as XII or XX. This expectation is supported in part by the early studies on *trans* β -benzoylacrylic acid and nuclear-substituted analogs where the *cis* forms have been so far obtained only in the esters and not in the free acids themselves (2).

trans β -(4-Bromobenzoyl)acrylic acid (I) has been made from maleic anhydride by the Friedel-Crafts reaction (3), and it has the normal properties expected of the type. It forms an acid chloride, dissolves in sodium bicarbonate, reacts with strong alkali to undergo self-condensation, is reduced readily to the saturated ketonic acid (4), and can be converted into the methyl ester by diazo-methylation, by acid catalyzed methylation, by methanolysis of the acid chloride, and by the action of methyl iodide on the silver salt. The reaction with an excess of diazomethane proceeds beyond the ester formation, to produce the pyrazoline, which presumably has the structure VIII. Incidentally, it is noteworthy that this same pyrazoline was obtained also from the *cis* acid (II) and from both the *cis* and *trans* esters (III and IV), and that no stereo or structural isomer was detected, a result which is comparable with the similar pyrazoline formation from *cis* and *trans* dibenzoylethylenes (5).

Although the α -methyl derivative of the *trans* acid, I, readily undergoes rearrangement under the influence of sunlight to the *cis* isomer (1c), early attempts similarly to isomerize the *trans* β -aroylacrylic acids which are *without* ethylenic substituents have consistently failed (2a). This resistance to isomerization is in contrast to the susceptibility of the *trans* esters to this reaction. Conditions have now been found, however, under which the *trans* to *cis* inversion of the acids can be effected, and it involves simply the choice of a favorable solvent. In the case of I the favorable solvents are benzene and acetone, and in the case of β -benzoylacrylic acid itself, acetone. No inversion (of I) occurred in the solvents chloroform, ether, or ethanol, and exposure of the solid material to light, either as a dry powder or as a suspension in benzene, gave a polymer, pre-

¹ This paper is taken in part from a Doctorate Dissertation, University of Virginia, 1942.

² Holder of Philip Francis du Pont Fellowships 1940–1942. Present address, Jackson Laboratory, E. I. du Pont de Nemours & Co., Wilmington, Delaware.



sumably analogous to truxillic acid and to the polymer of β -(4-methoxybenzoyl)-acrylic acid (2c).

Ready solubilities of *cis* β -benzoylacrylic acid and the 4-bromo derivative (II) in sodium bicarbonate indicate these compounds to be actually, or to function, in the open-chain form and not in the cyclic or γ -hydroxylactone form. As was to be expected, the free *cis* acids are very labile and undergo rearrangement back to the *trans* forms readily. This transformation was effected by the action of dilute hydrochloric acid, sodium carbonate, sunlight on a chloroform solution containing a trace of iodine, or heating above the melting points.

A further test of the stability of the *cis* acid (II) under exposure to sunlight in chloroform, ether, or ethanol, was made to see if the failure to achieve *trans* to *cis* inversion in these solvents was due to instability or to side reactions. In ether and ethanol only part of the *cis* acid was recovered after 24 hours exposure, but no *trans* acid could be isolated, whereas in chloroform the product was mainly the *trans* isomer.

The *cis* acids are converted by diazomethane, and through the silver salts by methyl iodide, into the *cis* esters, which are readily obtainable also by the sunlight inversion of the *trans* esters. Methanol-sulfuric acid esterification, however, of the *cis* acid (II) produces the *trans* ester (III).

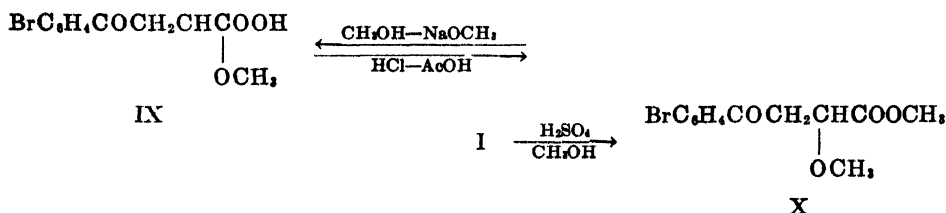
The hypothetical and as yet unknown *cis* acid chlorides are of particular interest in connection with ring-chain tautomerism. However, attempts to make the acid chloride of II failed. The reaction between the acid and phosphorus pentachloride at -35° evidently caused rearrangement before the acid chloride had formed completely, as shown by the production of a mixture of the *trans* acid chloride and the *trans* acid. The *trans* acid chloride on exposure to

sunlight in sodium-dried benzene gave only resinous products. From these results it appears unlikely that the *cis* acid chlorides can be made by the usual procedures.

The *trans* ester (III) seems to be definitely more easily isomerized to the *cis* isomer in the sunlight than is the *trans* acid (I), as shown by the fact that the transformation occurred in all of those solvents tried in which the *trans* acid was not affected, namely, chloroform, ether and ethanol.

Hydrogen chloride adds readily to *trans* β -bromobenzoylacrylic acid to give the expected addition compound, VII. This addition compound was converted back to the *trans* acid by treatment with sodium acetate in conc'd acetic acid.

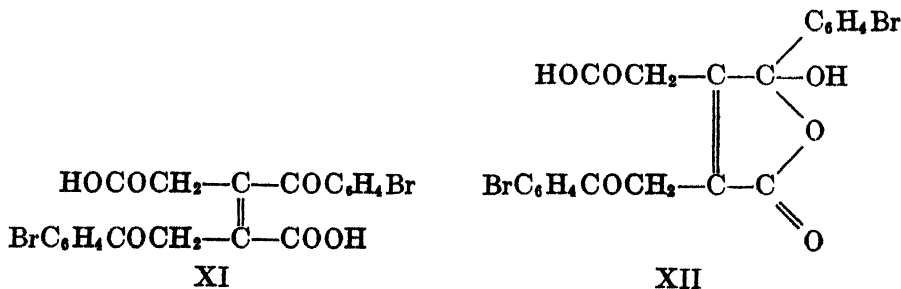
Sodium methoxide in methanol causes addition of methanol to the *trans* acid to give presumably the α -methoxy compound (IX), and this product is easily converted back to the *trans* acid by the action of a hydrochloric-acetic acid mixture. Methanol and sulfuric acid, by the method of Newman (6), converted the *trans* acid into the ester of a methanol addition product, presumably X.



The assumption that these addition reactions have placed the methoxyl in the α -position is suggested by analogy to *trans* β -(4-methoxybenzoyl)acrylic acid (2e), where the structure of such an addition compound has been demonstrated independently. These reactions are of interest in connection with the addition of alcohols to dibenzoylethylene, where the alkoxyfuran is the result (7).

The Structure of the Dimolecular Condensation Product

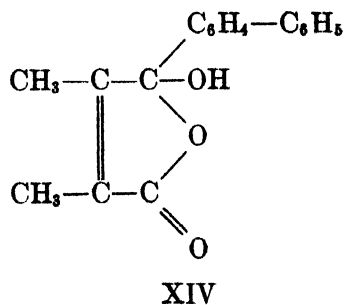
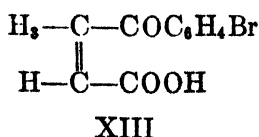
The attempt to hydrolyze both the *cis* and *trans* β -(4-bromobenzoyl)acrylic esters with alcoholic sodium hydroxide produced, instead of the expected *trans* acid, a dimolecular compound which can be obtained also from the *trans* acid under the same conditions. The compound was expected to be a self-condensation product of the type XI, possibly analogous to the cyclic compound obtained from dibenzoylethylene under similar conditions (8). Investigation of this compound leads us to believe that it has a quite different type of cyclic structure, however, namely, XII.



The evidence for a dibasic acid structure such as XI is the ready formation of a dimethyl ester; the evidence more specifically for the cyclic structure, XII, is the very weakly acidic character of one of these ester-forming groups. The neutral equivalent as determined by titration with standard alkali and phenolphthalein or thymolphthalein was 445 and 461, as compared with the theoretical of 510 for a monobasic acid and 225 for a dibasic acid. Obviously the second acidic group is very weakly acidic, although it responds to diazomethylation to give the dimethyl ester.

In a further investigation of the nature of the acidic groups, a potentiometric titration was carried out and the pH was plotted against standard alkali; this gave a first inflection point at about pH 6.9 and a second at about pH 9–10, and a neutral equivalent of 448 (as compared with the 510 calculated for the monobasic acid). The resulting solution, after this titration, was then treated with a small excess of standard alkali under refluxing to complete the conversion of the hydroxyfuranone carboxylic acid to the disodium salt; it was then cooled (to -5° to slow down cyclization of the dibasic acid when it was liberated), and was back-titrated with standard acid just beyond the first inflection point (at about pH 10) to determine the excess of alkali used. The solution was allowed to come to room temperature and the back-titration was continued beyond the end-point, which was assumed to cover the conversion of the disodium salt to the free dimolecular compound (XII); this gave a neutral equivalent of 285 as compared with the value of 255 for a dibasic acid. These results demonstrate the existence of the second and weakly acidic group, and support the hydroxyfuranone carboxylic acid structure XII.

The successful application of the potentiometric titration method above led us to undertake a similar study of two simpler compounds, in one of which this type of ring-chain tautomerism is involved. *cis* β -(4-Bromobenzoyl)- α -methylacrylic acid, which is believed to be open-chain (XIII), was titrated against standard alkali and back-titrated with standard acid. Both of these titrations gave normal curves in the plots against pH ; the midway inflection points fell at about pH 7 and the values of the neutral equivalents in two runs were 259 and 272 as compared with the calculated value of 269. This demonstrated a normal carboxyl group as formulated in XIII.

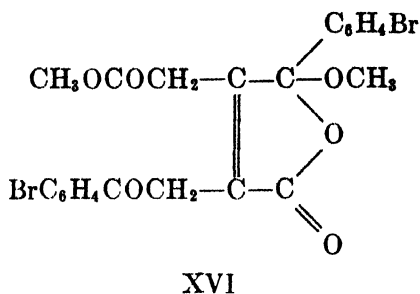
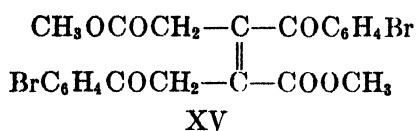


On the other hand, α,β -dimethyl- β -(*p*-xenoyl)acrylic acid (XIV) gave such a flat curve on direct and back-titrations, with the inflection points at pH 9 to

10, that an accurate determination of the neutral equivalent was not obtained; however, in the two titrations, values of 242 and 275 were obtained as compared with a theoretical of 247. This clearly indicates a very weakly acidic compound, and supports the cyclic structure which has been proposed on the basis of insolubility in sodium bicarbonate (1a).

Limited attempts to obtain further evidence for the cyclic structure of the dimolecular condensation product (XII) through characteristic reactions such as acylation and reduction, were not successful.

The compound (XII) reacts, as mentioned above, with diazomethane, with methanol-sulfuric acid, and through the silver salt with methyl iodide, to give the dimethyl ester apparently of a dibasic acid; and the diester is readily hydrolyzed back to the original dimolecular compound by hydrochloric and acetic acids. The open-chain formulation of the diester (XV) is preferred over the cyclic structure (XVI) in view of the mode of formation by diazomethane and through the silver salt by methyl iodide; however, it should be stressed that the cyclic structure, which might have been expected from a methanol-sulfuric acid esterification (1c), is not necessarily excluded on the basis of this evidence [*cf.* the diazomethylation of 4-benzoyl-2,5-diphenyl-2-hydroxyfuranone-3 (9)].

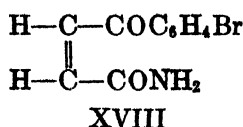
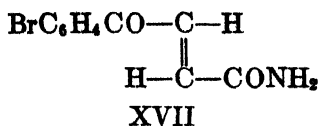


The structure of the dimolecular product is still, perhaps, open to some questions. It would appear from the fact of ring-chain tautomerism demonstrated above, that the condensation has gone unsymmetrically as formulated, because otherwise in neither of the two possible symmetrical modes of condensation would one have expected the product to have been capable of this type of ring-chain tautomerism. In the open-chain form there are two possible locations for the double bond, one of which would probably be the more stable because of the conjugation between carboxyl and 4-bromobenzoyl groups. The location indicated in the hydroxyfuranone structure XII, however, might well involve an equal or even stronger stabilizing influence; in any case it best accounts for the observed properties of the compound, especially the difficulty of reduction which is incompatible with an unsaturated 1,4-keto acid formulation.

As to the mechanism of the condensation reaction which leads to this product, two possibilities may be suggested: one, the enolization of the system to an allene enolate, followed by a Michael-type condensation with a second molecule; and the other, 1,4- addition of the elements of water or alkali to give an enolate, followed by a Michael-type condensation of this enolate with an unchanged molecule, and subsequent loss of a molecule of water or alkali (*cf.* 8b).

The Amides of the β -(4-Bromobenzoyl)acrylic Acids

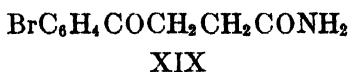
The primary amide of the *trans* acid (XVII) was made by the action of dry ammonia on a chloroform solution of the acid chloride. It had been determined previously that ammonia does not add to the conjugated system under these conditions as it had been found to do under other conditions (10).



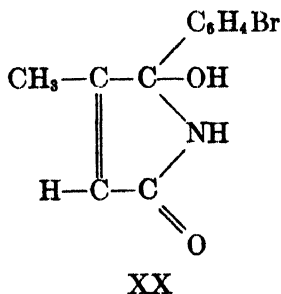
The *cis* amide (XVIII) could not be made as had been hoped through a *cis* acid chloride, but it is easily obtained by the sunlight inversion of the *trans* compound. It is in turn easily rearranged back to the *trans* isomer. The chloroform-iodine-sunlight combination which is usually used for this inversion gave amorphous products and a blue coloration; however, the inversion was readily accomplished by the action of dilute ethanol solution containing disodium phosphate.

Both the *cis* and *trans* amides were converted by methanol and hydrochloric acid into the *trans* ester (III). Hydrolysis by hydrochloric and acetic acids or by sodium acetate and acetic acid gave only intractable products; but the use of sulfuric and nitrous acids led to the formation of moderate yields of the *trans* acid.

Reduction of the *cis* and *trans* amides gave the expected saturated keto amide (XIX).



The *cis* amide (XVIII) is insoluble in sodium hydroxide in contrast to the α -methyl derivative which is soluble under these conditions (1g). This fact, coupled with the others outlined above, especially reduction and the facile interchange between the *cis* and *trans* forms, indicates that the *cis* compound is of the open-chain type, and not cyclic as the α -methyl derivative (XX) seems clearly to be.

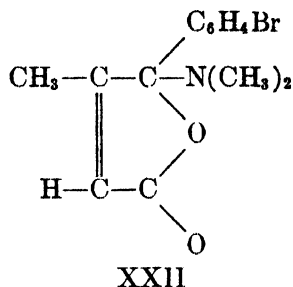
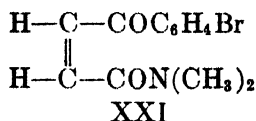


The reaction between aqueous methylamine and the *trans* acid chloride gave an alkali-soluble non-basic product of melting point 204° and empirical formula $\text{C}_{11}\text{H}_{12}\text{BrNO}_2$, which is to be investigated later.

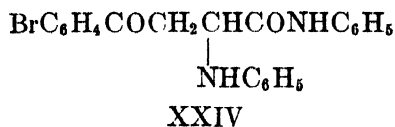
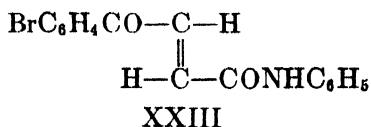
Dimethylamine in benzene solution converts the *trans* acid chloride into the *trans* amide, which is hydrolyzed to the *trans* acid by hydrochloric and acetic acids. This amide is reduced easily to the saturated keto amide. It is rearranged to the *cis* isomer by the action of sunlight on a solution in acetone, but not in the other solvents which were effective in the isomerization of the *trans* esters.

The *cis* dimethylamide was hydrolyzed by hydrochloric and acetic acids but gave the *trans* acid together with some *trans* amide; the latter product indicated that the configurational inversion preceded hydrolysis. The *cis* dimethylamide is quickly converted back into the *trans* isomer by the chloroform-iodine-sunlight combination.

From the foregoing facts it is clear that the *cis* dimethylamide is open-chain (XXI), and unlike the α -methyl analog which appears to be cyclic (XXII) (1g).



The *trans* acid chloride reacted in benzene with aniline to give two products, the anilide (XXIII), and the anilide addition product which is presumed to be XXIV.



The anilide (XXIII) was easily reduced to the saturated compound. Hydrolysis led to intractable products, but methanolysis led to a new and unknown compound (see experimental part). Repeated attempts to isomerize it by the action of sunlight failed.

The *trans* acid chloride reacted with N-methylaniline to give exclusively the N-methylanilide without further addition such as occurred with aniline. It was reduced to the saturated amide, which was made also from the saturated ester by the action of N-methylanilinomagnesium bromide. Like the anilide, the N-methyl derivative could not be isomerized to the *cis* form, and resisted hydrolysis and methanolysis. The action of hydrochloric and acetic acids, however, produced a new compound, the analysis of which indicated the empirical formula $\text{C}_{17}\text{H}_{14}\text{BrNO}_2$; this and the possibly analogous compounds obtained from the anilide (above) and from the N-methylanilide in the α -methyl series,³ are still to be investigated.

³ See Ref. 1g, page 195-196.

The foregoing studies obviously have been limited because of the non-availability of the *cis* acid chloride, and it is hoped that a way may yet be found to make this interesting compound.

EXPERIMENTAL PART⁴

trans β -(4-Bromobenzoyl)acrylic acid (I) was prepared by a modification of the procedure of Kohler and Woodward (3), by adding maleic anhydride to a mixture of bromobenzene, aluminum chloride, and tetrachloroethane (35°) and heating for two hours on a water-bath at 45–52°; yield 74%; recrystallized from benzene.

The acid chloride (3) was made by the action of phosphorus pentachloride on a carbon disulfide solution; crystallized from isooctane; melting point 104–104.5°.

trans Methyl β -(4-bromobenzoyl)acrylate (III) was made in the following ways: (a) The *trans* acid chloride was reacted with methanol (20 hours at room temperature). (b) An ether solution of less than the calculated amount of diazomethane was added slowly to a sample of the acid; the unchanged acid was recovered by extraction with sodium bicarbonate [the production of the pyrazoline (VIII) was minimized by this procedure]. (c) A solution of the acid in sodium bicarbonate was treated with silver nitrate and the precipitated silver salt was filtered, suspended in methanol and methyl iodide, and the mixture refluxed for ten minutes. The silver iodide was filtered and the solution diluted with water to precipitate the ester. (d) A solution of the *trans* acid in saturated methanolic hydrogen chloride was allowed to stand for 12 hours. Neutralization with 5% sodium carbonate gave an oil which was purified by evaporation at 131° under 8 mm. onto a cold-finger condenser (the yield was poor). (e) A solution of the acid in methanol containing a small amount of conc'd sulfuric acid was refluxed for 2.5 hours.

The ester was crystallized from dilute methanol; melting point 77°.

Anal. Calc'd for $C_{11}H_9BrO_3$: C, 49.10; H, 3.37. Found: C, 48.72; H, 3.37.

Hydrolysis of the ester was effected in a 4:10 by volume mixture of conc'd hydrochloric and acetic acids upon refluxing for one hour.

cis β -(4-Bromobenzoyl)acrylic acid (II). A solution of 21 g. of the *trans* acid (I) in 700 ml. of acetone was exposed to sunlight for 60 hours. Approximately 100 ml. of this solution was evaporated in a current of air and the white residue was recrystallized from benzene; yield 2.2 g.; melting point, 129°, solidifying at 133° and melting again at 162°.

Anal. Calc'd for $C_{10}H_7BrO_3$: C, 47.08; H, 2.77. Found: C, 47.00; H, 3.02.

The remainder of the original solution after similar treatment and recrystallization from benzene gave largely the *trans* acid.

To avoid this extensive reversion to the *trans* acid during purification, the crude *cis* acid was dissolved quickly in already-boiling benzene, and the solution was immediately and rapidly filtered and cooled.

The sunlight inversion worked equally well in benzene as solvent.

The *cis* acid is soluble in sodium bicarbonate or carbonate and is recovered without isomerization upon acidification with 6 N hydrochloric acid.

Rearrangement to the *trans* acid was effected as follows: (a) heating in benzene solution (b) suspending in benzene containing a trace of hydrochloric acid, for ten minutes; and (c) exposure of a solution in chloroform to sunlight for 24 hours. Attempts to make a *cis* acid chloride with phosphorus pentachloride in carbon disulfide at –35° gave only *trans* products. Exposure of samples of the *cis* acid in ether and in 95% ethanol to sunlight for 24 hours gave considerable non-crystalline material and some unchanged *cis* acid, but none of the *trans* compound.

cis Methyl β -(4-bromobenzoyl)acrylate (IV) was prepared as follows: (a) A solution of the *trans* ester in benzene was exposed to sunlight for 15 hours. (b) An ethereal solution of diazomethane was added to a slight excess of the acid (II), and the unchanged acid was

⁴ All melting points are "corrected".

removed by sodium bicarbonate. (c) A solution of the *cis* acid in 5% sodium carbonate was neutralized with acetic acid, and treated with silver nitrate to precipitate the silver salt which was filtered and treated with methanol and methyl iodide for 3 hours.

The ester was crystallized repeatedly from dilute ethanol. It melted at 56.5°.

Anal. Calc'd for $C_{11}H_{13}BrO_2$: C, 49.10; H, 3.37. Found: C, 49.19; H, 3.65.

Rearrangement to the trans ester was effected by exposure of a chloroform solution containing a trace of iodine to sunlight for 15 hours.

Attempted hydrolysis by solution at room temperature in 100% sulfuric acid (several minutes) and pouring into crushed ice, gave unchanged *cis* ester.

β -(4-Bromobenzoyl)propionic acid (V) was obtained by zinc dust-conc'd acetic acid reduction (2 minutes at boiling temperature) of samples of both the *cis* and *trans* acids, and the product (m.p. 149°) was identified by mixture melting point with an authentic sample (4).

β -(4-Bromobenzoyl)propionic acid methyl ester (VI) was made by the following procedures: (a) An excess of ethereal diazomethane was added to a sample of the acid (V). (b) A mixture of the *cis* or *trans* esters with 70% ethanol was treated with an excess of sodium hydrosulfite with refluxing for one hour and dilution with water.

It was recrystallized repeatedly from dilute ethanol and melted at 51.5°.

Anal. Calc'd for $C_{11}H_{11}BrO_2$: C, 48.73; H, 4.09. Found: C, 48.62; H, 4.17.

β -(4-Bromobenzoyl)- α -chloropropionic acid (VII). A suspension of the *trans* acid (I) in conc'd hydrochloric acid, after standing for 36 hours, gave a flocculent mass at the top of the solution, which was decanted from unchanged material at the bottom. It was recrystallized from benzene, and melted at 129.5°.

Anal. Calc'd for $C_{10}H_8BrClO_2$: C, 41.23; H, 2.76. Found: C, 41.07; H, 3.00.

Elimination of hydrogen chloride was effected by the action of a refluxing 5% solution of sodium acetate in conc'd acetic acid for 15 minutes; the *trans* acid (I) was recovered and identified.

β -(4-Bromobenzoyl)- α -(*p*)-methoxypropionic acid (IX). One gram of the *trans* acid (I) was added to a solution of 0.16 g. of sodium in 25 ml. of methanol; after standing 16 hours the mixture was diluted with water and neutralized with 6 *N* hydrochloric acid. The product was crystallized from benzene; yield 0.63 g. (63%); melting point 115.6°.

Anal. Calc'd for $C_{11}H_{11}BrO_4$: C, 46.01; H, 3.86. Found: C, 46.25; H, 4.02.

Elimination of methanol was effected by the action of a 4:10 by volume mixture of conc'd hydrochloric and acetic acids (refluxing for 30 minutes). The *trans* acid (I) was recovered and identified by mixture melting point.

β -(4-Bromobenzoyl)- α -(*p*)-methoxypropionic acid methyl ester (X). A solution of 1.29 g. of the *trans* acid in 16 ml. of 100% sulfuric acid, after standing for seven minutes, was poured into ice-cold methanol [cf. method of Newman (6)]. Dilution with water, extraction with ether, washing with sodium carbonate, evaporation of the solvent and evaporation of the residue at 120–130° and 2–3 mm. pressure onto a cold-finger condenser, gave 1.27 g. of product. Repeated crystallization from petroleum ether gave long needles of melting point 44–45°.

Anal. Calc'd for $C_{12}H_{13}BrO_4$: C, 47.85; H, 4.35; OCH_3 , 20.60. Found: C, 47.79; H, 4.55; OCH_3 , 19.69.

4-(4-Bromobenzoyl)-3-carbomethoxy-pyrazoline (VIII). Samples of the *cis* and *trans* acid and esters were added in each case to solutions of an excess of diazomethane in ether and allowed to stand until the reactions appeared to be complete. The products were the same; the compound was crystallized from dilute methanol or ethanol; melting point 120–121°.

Anal. Calc'd for $C_{12}H_{11}BrN_2O_2$: C, 46.32; H, 3.56; N, 9.01. Found: C, 46.58; H, 2.88; N, 8.76.

Di-(4-bromobenzoyl)-dicarboxycyclobutane [dimer of β -(4-bromobenzoyl)acrylic acid]. A suspension of 2 g. of the *trans* acid (I) in 150 ml. of benzene was exposed for eight hours to sunlight. Upon heating to boiling, solution occurred and on cooling 0.57 g. (28%) of the dimer crystallized as colorless plates. Recrystallization from ethanol brought the melting

point to 249°. Exposure to sunlight for 36 hours, of the powdered solid, held between two plates of glass, gave the same compound.

Anal. Calc'd for $C_{20}H_{14}Br_2O_6$: C, 47.08; H, 2.76; mol. wt. 510. Found: C, 46.84; H, 2.91; mol. wt. 456.

Sublimation at 150° at 7 mm. pressure gave the *trans* acid (I) in small yield.

The dimolecular condensation product, 3-(4-bromophenacyl)-4-carboxymethyl-5-hydroxy-5-(4-bromophenyl)furanone-2 (XII). A suspension of 15 g. of the *trans* acid (I) in 528 ml. of 4% sodium hydroxide was stirred for 1.5 hours. Acidification gave 10.4 g. (67%) of XII. Hydrolysis of samples of both the *cis* and *trans* esters (IV and III) by sodium hydroxide in 40% ethanol (20 hours at room temperature) gave this same product. It crystallized as elongated rectangular plates from dilute ethanol and melted at 177.5°. It could also be crystallized from 95% ethanol or ethyl acetate.

Anal. Calc'd for $C_{20}H_{14}Br_2O_6$: C, 47.08; H, 2.76; Neut. eq. 510. Found: C, 46.95; H, 2.82. Neut. eq. 460.

This compound was not changed upon treatment with (a) phosphorus pentachloride at room temperature followed by hydrolysis; (b) conc'd sulfuric acid, dissolving at room temperature; (c) conc'd acetic and hydrochloric acids (at 150–160° for 4 hours); (d) conc'd acetic acid, red phosphorus, and iodine [according to Fuson and Grey (11)]; (e) stannous chloride in conc'd acetic and hydrochloric acids (refluxing for 30 minutes); (f) sunlight on an acetone solution, for 4 days; and (g) acetic anhydride or acetyl chloride plus a small amount of conc'd sulfuric acid (one hour at room temperature).

Only intractable products were obtained upon vacuum distillation, heating with phosphorus pentachloride at 100°, heating with phosphorus pentoxide at 100°, and treatment with sodium hydrosulfite in solution in 5% sodium carbonate (refluxing for one hour). Some of these experiments were tried because at first the compound was thought to be the α -hydroxy acid resulting from water addition.

Potentiometric titrations with standard sodium hydroxide and back-titrations with standard hydrochloric acid were carried out, using a Beckman pH meter.

The dimethyl ester (XV or XVI) of the condensation product (XII), was prepared (a) by the action of an excess of ethereal diazomethane; (b) by the action of 25 ml. of methanol and 2.5 ml. of conc'd sulfuric acid (refluxing for one hour) on 1.5 g. of XII; yield 1.34 g.; (c) as follows: a suspension of 1 g. of the acid (XII) in 1 ml. of 10% sodium hydroxide was diluted with 25 ml. of methanol; 5 ml. of 1 N silver nitrate was added; the precipitate was filtered, suspended in a mixture of 40 ml. of methanol and 4 ml. of methyl iodide, and the mixture was refluxed for 20 minutes and filtered; evaporation of the filtrate in a current of air gave a solid which was crystallized from methanol; yield 0.3 g.; and (d) by a procedure similar to (c) but using the *cis* acid (II) which is evidently condensed to XII under the influence of the strong alkali.

The three samples prepared above were shown to be identical by mixture melting point. The compound was purified by repeated crystallizations from dilute ethanol and melted at 121°.

Anal. Calc'd for $C_{22}H_{18}Br_2O_6$: C, 49.10; H, 3.37; mol. wt. 538. Found: C, 49.10; H, 3.78; mol. wt. 506.

Hydrolysis by a 4:10 by volume mixture of conc'd hydrochloric and acetic acids (refluxing for one hour) regenerated XII which was identified by mixture melting point.

The compound (XV) was recovered unchanged (a) after treatment with sodium hydrosulfite in 70% ethanol (refluxing for one hour), and (b) upon exposure in acetone solution for 4 days to the action of sunlight.

trans β -(4-Bromobenzoyl)acrylic amide (XVII). Dry ammonia was bubbled through a 100-ml. chloroform solution of 14.5 g. of *trans β -(4-bromobenzoyl)acrylyl chloride* for one hour. The resulting yellow crystalline precipitate was recrystallized from ethanol; yield 8 g.; the melting point after repeated crystallizations was 185° decomp.

Anal. Calc'd for $C_{10}H_8BrNO_2$: N, 5.51. Found: N, 5.50.

This amide was insoluble in 10% sodium hydroxide. It gave a purple coloration and

intractable product upon attempted hydrolysis by conc'd acetic and hydrochloric acid mixture, and by sodium acetate in conc'd acetic acid (heating). *Hydrolysis* was effected as follows: one gram of the amide in 10 ml. of cold conc'd sulfuric acid was treated with 1 g. of sodium nitrite in 5 ml. of water, and the mixture was warmed on the water-bath till the evolution of gas ceased. The resulting precipitate was crystallized from benzene (0.6 g.) and identified upon repeated crystallization as largely the *trans* acid. (This procedure with an excess of the reagent applied directly to the *trans* acid gave chiefly 4-bromobenzoic acid).

Methanolysis of the amide was effected by a 3:50 by volume mixture of conc'd hydrochloric acid and methanol under refluxing for 1.9 hours. The main product was a tar from which the *trans* acid was isolated in small amounts by vacuum evaporation at 157°.

trans β -(4-Bromobenzoyl)acrylic dimethylamide, $BrC_6H_4COCH=CHCON(CH_3)_2$. Dry dimethylamine was absorbed in a benzene solution of the *trans* acid chloride. The product crystallized as yellow rectangular plates from 33% ethanol; melting point 118–119.5°.

Anal. Calc'd for $C_{11}H_{11}BrNO_2$: N, 4.96. Found: N, 4.90.

It was insoluble in sodium hydroxide and hydrochloric acid. *Hydrolysis* by 1:10 by volume conc'd hydrochloric and acetic acids (refluxing for 20 hours) gave the *trans* acid (I). Hydrolysis with 10% sodium hydroxide (15 days at room temperature) gave a compound of melting point 183–196° which was not investigated.

trans β -(4-Bromobenzoyl)acrylic anilide (XXIII) was prepared from 40 g. of the *trans* acid chloride and 32.8 g. of aniline in 250 ml. of benzene (34 hours at room temperature). The crude solid precipitate was crystallized from benzene (9.5 g.); pale yellow needles; melting point 196–197°.

Anal. Calc'd for $C_{16}H_{12}BrNO_2$: N, 4.67. Found: N, 4.59.

The benzene filtrates gave the anilide addition compound, β -(4-bromobenzoyl)- α (β)-(N-phenylamino)propionic anilide (XXIV), as a solid, which was purified by leaching with ethanol; 10.8 g. of melting point 146–147.5°. Further leaching with boiling ethanol left colorless needles of melting point 163–164°.

Anal. Calc'd for $C_{22}H_{18}BrN_2O_2$: N, 6.62. Found: N, 6.93.

The *trans* anilide (XXIII) was insoluble in sodium hydroxide. Hydrolysis under a variety of conditions gave intractable products. Attempts at sunlight inversion in acetone, methanol, and ethanol failed.

The action of saturated methanolic hydrogen chloride under an atmosphere of nitrogen, refluxing for 6 hours, gave a small yield of a new compound; it crystallized as fine yellow platelets from methanol; melting point 178.5–179°.

Anal. Calc'd for $C_{17}H_{14}BrNO_2$: C, 59.32; H, 4.10. Found: C, 58.75; 59.15; H, 4.17; 4.18.

trans β -(4-Bromobenzoyl)acrylic N-methylanilide, $BrC_6H_4COCH=CHCON(CH_3)C_6H_5$, was prepared from 12 g. of the *trans* acid chloride by interaction with 10 ml. of methylaniline in 100 ml. of acetone (12 hours at room temperature). Dilution with ice-water gave a product which was crystallized from ethanol; 12.9 g.; yellow trapezoidal prisms; melting point 138–140°.

Anal. Calc'd for $C_{17}H_{14}BrNO_2$: N, 4.07. Found: N, 4.06.

Attempts at hydrolysis with acids and inversion by the action of sunlight failed.

The action of conc'd hydrochloric and acetic acids (a 1:8 mixture by volume) under reflux for 15 hours gave a yield of about 50% of a new compound which was purified by repeated crystallizations from 70% ethanol; colorless needles of melting point 158°.

Anal. Calc'd for $C_{17}H_{14}BrNO_2$: C, 59.32; H, 4.10; N, 4.07. Found: C, 59.04; H, 4.50; N, 4.12; 4.02.

This compound was insoluble in 10% sodium hydroxide; it was not changed upon treatment with (a) sodium acetate in conc'd acetic acid (refluxing for 4 hours), (b) stannous chloride in conc'd hydrochloric and acetic acids, and (c) ethereal diazomethane. Oxidation by potassium permanganate of a suspension of 0.15 g. of the compound in 10% sodium hydroxide gave a 46% yield of 4-bromobenzoic acid.

cis β -(4-Bromobenzoyl)acrylic amide (XVIII). A solution of 3.69 g. of the *trans* amide (XVII) in 225 ml. of ethanol, exposed to sunlight for 7 hours, and evaporated in a current

of air, gave a colorless residue which was crystallized from benzene; yield, 3.45 g.; the melting point after further crystallizations from chloroform was 130–135° decomp.

Anal. Calc'd $C_{15}H_{13}BrNO_2$: C, 47.27; H, 3.17; N, 5.51. Found: C, 47.12; H, 3.49; N, 5.27.

The compound was insoluble in 10% sodium hydroxide. It was resinified by the action of sunlight in a chloroform solution containing iodine. *Inversion* to the *trans* amide was accomplished by the action of a 10% solution of disodium phosphate in 70% ethanol (refluxing for 50 minutes). *Hydrolysis* by sulfuric acid and sodium nitrite (as with the *trans* amide) gave a low yield of the *trans* acid and a considerable amount of 4-bromobenzoic acid. *Methanolysis* by saturated methanolic hydrogen chloride (12 hours at room temperature) gave a small yield of the *trans* ester.

cis β -(Bromobenzoyl)acrylic *N*-dimethylamide, (XXI), was prepared by the action of sunlight for 20 days on an acetone solution of the *trans* compound. The reaction was not successful in methanol or ethanol. The compound was crystallized from a benzene-ligroin mixture; melting point 77.5–78.5°.

Anal. Calc'd for $C_{15}H_{13}BrNO_2$: C, 51.08; H, 4.29. Found: C, 51.29; H, 4.53.

The compound is insoluble in 10% sodium hydroxide, is converted back to the *trans* isomer by the action of sunlight on a chloroform-iodine solution, and is converted to a mixture of the *trans* acid and *trans* amide by the action of conc'd hydrochloric and acetic acids (1:10 by volume, refluxing for 5 hours).

β -(4-Bromobenzoyl)propionic amide (XIX). (a) Raney nickel hydrogenation at atmospheric pressure and room temperature, of samples of the *trans* amide, in ethanol, gave XIX in 70% yield. (b) Reduction of the *cis* amide under the same conditions, and also by sodium hydrosulfite in 70% ethanol (refluxing for 45 minutes), gave 10% yields only of XIX. It crystallized as rectangular plates melting at 174–175°.

Anal. Calc'd for $C_{10}H_{10}BrNO_2$: N, 5.47. Found, N, 5.62.

Hydrolysis with 1:10 by volume conc'd hydrochloric and acetic acids (refluxing for 2 hours) gave the acid V.

β -(4-Bromobenzoyl)propionic *N*-dimethylamide, $BrC_6H_4COCH_2CH_2CON(CH_3)_2$. (a) Reduction of either the *cis* or *trans* *N*-dimethylamides by adding a solution of the amide in a small amount of ethyl acetate to a mixture of an excess of stannous chloride in a 1:2 conc'd hydrochloric-acetic acid mixture (room temperature for one hour) gave the saturated amide in 92 and 90% yields respectively. (b) Reduction of the *trans* amide by sodium hydrosulfite in 70% ethanol (refluxing) gave a small yield of the saturated amide and a large amount of a sulfur-containing water-soluble compound of melting point above 237°; the latter compound evidently is a bisulfite addition compound, and was not investigated.

Repeated crystallizations of the saturated amide from benzene-ligroin mixtures gave colorless rectangular plates of melting point 106–107°.

Anal. Calc'd for $C_{15}H_{14}BrNO_2$: C, 50.72; H, 4.97. Found: C, 50.95; H, 5.44.

Hydrolysis as above gave the saturated acid.

β -(4-Bromobenzoyl)propionic anilide, $BrC_6H_4COCH_2CH_2CONHC_6H_5$, was made in nearly quantitative yield by the stannous chloride reduction method described above; it crystallized as needles from ethanol; melting point 145–146°.

Anal. Calc'd for $C_{18}H_{14}BrNO_2$: N, 4.22. Found: N, 3.93.

Hydrolysis by a 1:10 conc'd hydrochloric-acetic acid mixture (refluxing for 16 hours) gave the acid (V).

β -(4-Bromobenzoyl)propionic *N*-methylanilide, $BrC_6H_4COCH_2CH_2CON(CH_3)C_6H_5$, was obtained in 90% yield by the action of sodium hydrosulfite in 70% ethanol under refluxing for one hour, and in 85% yield upon stannous chloride reduction by the method described above. It was made also in small yield by a modification of the method of Kuhn (12, 1g) by the action of *N*-methylanilinomagnesium bromide in ether and benzene. It crystallized from 60% ethanol as rectangular needles melting at 101.5–103°.

Anal. Calc'd for $C_{17}H_{14}BrNO_2$: N, 4.05. Found: N, 4.03.

Hydrolysis by 1:10 by volume conc'd hydrochloric-acetic acids (refluxing for 5 hours) gave incomplete hydrolysis to the acid (V).

cis β -Benzoylacrylic acid. A solution of 1 g. of *trans* β -benzoylacrylic acid in 30 ml. of

acetone was exposed to sunlight for 15 hours and evaporated under a current of air. The white residue crystallized as fine needles from benzene and melted at 84.5°.

Anal. Calc'd for $C_{10}H_8O_2$: C, 68.18; H, 4.50. Found: C, 67.98; H, 4.38.

Inversion back to the *trans* isomer was effected by (a) exposure of a chloroform solution, containing a trace of iodine, to sunlight; (b) heating a sample to 100°; (c) solution in 5% sodium carbonate and liberation by 6 *N* hydrochloric acid and extraction with ether; and (d) suspension in benzene containing a trace of conc'd hydrochloric acid.

Esterification to the *cis* ester was effected by the action of the calculated amount of standardized ethereal diazomethane, extraction of unreacted acid by 5% sodium carbonate, and evaporation of the solvent. Acidification of the carbonate solution gave a small amount of *trans* acid which must have been the result of isomerization of that part of the *cis* acid which had escaped methylation.

SUMMARY

β -Benzoyl and β -(4-bromobenzoyl)acrylic acids have been obtained in the very labile *cis* forms. These are methylated by diazomethane to the esters.

β -(4-Bromobenzoyl)acrylic acid reacts with an excess of diazomethane to give the pyrazoline. Hydrogen chloride and methanol addition products have been obtained.

The action of alkali produced a dimolecular condensation product which appears to be a hydroxyfuranone carboxylic acid. Potentiometric titrations demonstrated the ring-chain tautomerism of this product. It gave a dimethyl ester.

The β -(4-bromobenzoyl)acrylic amide and *N,N*-dimethylamide were made and converted by the action of sunlight into *cis* isomers. The anilide and *N*-methylanilide were also prepared but these could not be obtained in *cis* forms.

The evidence accumulated leads to the conclusion that the *cis* β -aroylacrylic acids and amides, without substituents on the ethylene linkage, are open-chain and will not easily, if at all, react in the sense of the cyclic forms.

CHARLOTTESVILLE, VIRGINIA

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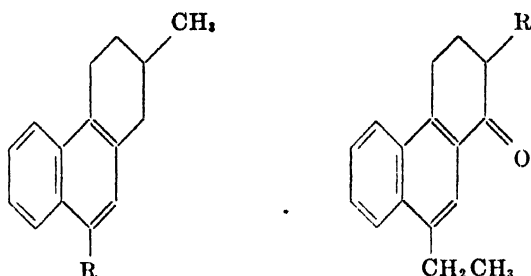
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REACTIONS OF 1,2,3,4-TETRAHYDROPHENANTHRENE AND DERIVATIVES. V. 2-METHYL-1,2,3,4-TETRAHYDROPHENANTHRENE

W. E. BACHMANN AND A. G. ANDERSON, JR.¹*Received November 24, 1947*

In continuation of the work on the reactions of 1,2,3,4-tetrahydrophenanthrene and its derivatives (1), 2-methyl- and 2-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene have been synthesized and subjected to a modified Friedel-Crafts reaction with acetyl chloride. From the products, various new derivatives of tetrahydrophenanthrene have been prepared.

2-Methyl-1,2,3,4-tetrahydrophenanthrene was synthesized from β -1-naphthylethyl bromide, which upon condensation with sodiomalonic ester yielded ethyl β -1-naphthylethyl malonate. The sodio derivative of the latter was condensed with methyl iodide to give ethyl methyl- β -1-naphthylethyl malonate, which upon hydrolysis to the corresponding dicarboxylic acid and subsequent decarboxylation, afforded α -methyl- γ -1-naphthylbutyric acid. Treatment of the acid with phosphorus pentachloride and cyclization of the resultant acid chloride with anhydrous stannic chloride gave 1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene, which was readily reduced by the Clemmensen method to the desired 2-methyltetrahydrophenanthrene (I). The structure of this hydrocarbon was proved by dehydrogenation to the known 2-methylphenanthrene.



- | | | |
|---|---|-------------------------------|
| I, R = H | Ic, R = CH ₂ CONH ₂ | IIa, R = H |
| Ia, R = COCH ₃ | If, R = CH ₂ COOH | Iib, R = COCOOCH ₃ |
| Ib, R = CH ₂ CH ₃ | Ig, R = NHCOCH ₃ | Iic, R = COOCH ₃ |
| Ic, R = COCH ₂ Br | Ih, R = NH ₂ | IId, R = CH ₃ |
| Id, R = COOH | | |

Acetylation of 2-methyl-1,2,3,4-tetrahydrophenanthrene in a mixture of tetrachloroethane and carbon disulfide gave the 9-acetyl derivative (Ia). Bachmann and Cronyn (2) found that 1,2,3,4-tetrahydrophenanthrene substituted predominantly in the 9-position under the same conditions. The 9-acetyl compound was reduced by the Clemmensen method to 2-methyl-9-ethyl-1,2,3,4-

¹ From the Ph.D. dissertation of A. G. Anderson, Jr. Present address: Department of Chemistry, University of Washington, Seattle, Washington.

tetrahydrophenanthrene (Ib), and the structure of this compound proved by synthesis from the known 1-keto-9-ethyl-1,2,3,4-tetrahydrophenanthrene (IIa). Treatment of the cyclic ketone with dimethyl oxalate in the presence of sodium methoxide produced 1-keto-9-ethyl-1,2,3,4-tetrahydrophenanthrene-2-glyoxalate (IIb) which was decarbonylated to 1-keto-2-carbomethoxy-9-ethyl-1,2,3,4-tetrahydrophenanthrene (IIc) in the presence of powdered glass. The sodio derivative of the β -keto ester was treated with methyl iodide and the resulting 1-keto-2-methyl-2-carbomethoxy derivative was hydrolyzed and decarboxylated to 1-keto-2-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene (IId). Reduction of the keto group afforded 2-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene (Ib) which was identical with the material obtained by the reduction of the 2-methyl-9-acetyl compound.

Bromination of 2-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene yielded the 9-bromoacetyl derivative (Ic). Oxidation of the acetyl derivative with sodium hypochlorite gave the corresponding 9-carboxylic acid (Id). Hydrolysis of the acid amide (Ie) obtained by a Willgerodt reaction on the 9-acetyl derivative gave 2-methyltetrahydrophenanthrene-9-acetic acid (If). Beckmann rearrangement of the oxime of the 9-acetyl compound afforded the 9-acetylamino derivative (Ig) which was hydrolyzed to 2-methyl-9-aminotetrahydrophenanthrene (Ih).

Acetylation of 2-methyl-9-ethyltetrahydrophenanthrene gave what is probably 2-methyl-7-acetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene, since Friedel-Crafts substitution of tetrahydrophenanthrene is known to occur at the 7-position when the 9-position is occupied by an alkyl group (3). Bromination of the ketone gave the corresponding bromoacetyl compound.

Reduction of the oxime of 1-keto-9-ethyltetrahydrophenanthrene by 2% sodium amalgam gave 1-amino-9-ethyl-1,2,3,4-tetrahydrophenanthrene in good yield.

EXPERIMENTAL

*α -Methyl- γ -1-naphthylbutyric acid.*² Absolute alcohol (15 ml.) was added to 0.85 g. of sodium covered with dry benzene. After all of the sodium had reacted, the contents were cooled, 10.1 g. of β -1-naphthylethylmalonic ester (4) was added, and the mixture was refluxed for thirty minutes. To the cooled mixture 2.98 g. (1.3 ml.) of methyl iodide was added followed by swirling. After the mixture had stood at room temperature overnight, a second equal portion of methyl iodide was added. At the end of thirty minutes standing with occasional swirling, the mixture was refluxed for three hours, [the diethyl methyl- β -1-naphthylethylmalonate may be isolated; yield, 10.1 g. (96%); b.p. 160–165° at 0.03 mm.] and poured into a solution of 11.5 g. of potassium hydroxide in 18 ml. of water and 6 ml. of ethanol. After the vigorous reaction had subsided, the alcohol and benzene were removed in a current of air, water was added until the solution became cloudy, and the mixture was heated on a steam-bath for one hour. After it had been cooled and extracted with benzene the aqueous solution was added slowly with stirring to a solution of 28 ml. of hydrochloric acid in 15 ml. of water. The methyl- β -1-naphthylethylmalonic acid precipitated as a fluffy mass of colorless needles; weight after drying over phosphorus pentoxide

² After our work had been completed, Wilds and Beck, *J. Am. Chem. Soc.*, **66**, 1690 (1944), reported the preparation of this compound by essentially the same method except that they used methyl bromide.

for eight hours, 8.49 g.; m.p. 180–181° with evolution of gas. It had the neutral equivalent 136 (calculated: 136).

The crude dicarboxylic acid from the reaction of 8.3 g. of sodium dissolved in 105 ml. of absolute ethanol, 94.2 g. of ethyl- β -naphthylethyl malonate and 60 g. of methyl iodide was decarboxylated by heating at 200° until the evolution of carbon dioxide had ceased, and the hot liquid was poured into 20 ml. of glacial acetic acid, an additional 25 ml. of acid being used to rinse the flask. After adding water until the solution became cloudy, the mixture was heated until clear and allowed to cool slowly. The α -methyl- γ -1-naphthylbutyric acid separated as fine needles; yield 62.5 g. (91.4%); m.p. 81–83°. Three recrystallizations of a sample from 30–60° petroleum ether gave fine colorless needles melting at 84–86°; further recrystallization did not raise the melting point. Haworth (5), who prepared this compound by a different method, reported the melting point 89–90°.

Anal. Calc'd for $C_{16}H_{18}O_2$: C, 78.9; H, 7.1.

Found: C, 78.7; H, 7.0.

2-Methyl-1,2,3,4-tetrahydrophenanthrene (I). Inasmuch as our results on the cyclization of α -methyl- γ -1-naphthylbutyric acid differed only slightly from those reported later by Wilds and Beck (see Footnote 2), the details of the experiment are omitted. From 117 g. of the acid as obtained from the aqueous acetic acid solution we obtained 99 g. (91.9%) of recrystallized (from methanol) 1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene with the m.p. 67–72° and 3 g. (2.5%) of less pure material (m.p. 57–66°).

Reduction of 50 g. of the crude cyclic ketone by the method described for the reduction of 1- and 4-ketotetrahydrophenanthrene (6) gave 42.9 g. (91.7%) of crude 2-methyl-1,2,3,4-tetrahydrophenanthrene (b.p. 117–125° at 0.1 mm.), which crystallized on cooling. Recrystallization from benzene-petroleum ether and then from ethanol yielded 39.9 g. (85.3%) of colorless platelets; m.p. 58–58.5°.

Anal. Calc'd for $C_{18}H_{18}$: C, 91.8; H, 8.2.

Found: C, 91.6; H, 8.6.

An 0.88-g. sample of the above hydrocarbon was heated with 0.2 g. of palladium-charcoal catalyst (7) for thirty minutes at 300–310° in an atmosphere of nitrogen. The process was repeated with an additional 0.05 g. of the catalyst, acetone was added, the catalyst removed by filtration, and the solvent evaporated. The residual solid, after evaporative distillation under reduced pressure and recrystallization from alcohol, gave colorless needles of 2-methylphenanthrene; m.p. 56.5–57.5° alone and when mixed with an authentic sample.

2-Methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene (Ia). As described by Bachmann and Cronyn (2) for the preparation of 9-acetyl-1,2,3,4-tetrahydrophenanthrene, 84.5 g. of the aforementioned 2-methyltetrahydrophenanthrene was converted into the 2-methyl-9-acetyl derivative in 77.5% yield (79.5 g.) of colorless needles; m.p. 79–80°. No attempt was made to isolate any isomeric product that might have been present.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.7; H, 7.6.

Found: C, 85.3; H, 7.7.

Methyl 1-keto-9-ethyl-1,2,3,4-tetrahydrophenanthrene-2-glyoxalate (IIb). When treated with dimethyl oxalate by the procedure of Bachmann, Cole, and Wilds (8), 17 g. of crude 1-keto-9-ethyltetrahydrophenanthrene (IIa) (6) yielded 13.48 g. (57%) of product after recrystallization from methanol-acetone; m.p. 104–105°.

Anal. Calc'd for $C_{19}H_{18}O_4$: C, 73.5; H, 5.9.

Found: C, 73.2; H, 6.1.

1-Keto-2-carbomethoxy-9-ethyl-1,2,3,4-tetrahydrophenanthrene (IIc). The above glyoxalate (11.42 g.) on decarbonylation with the aid of powdered glass (8) gave 9.45 g. (91%) of the β -keto ester as fine needles; m.p. 114–115°. Several recrystallizations of a sample from methanol-acetone raised the melting point to 122–123°. An alcoholic solution of the compound gave a deep green color with ferric chloride.

Anal. Calc'd for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4.

Found: C, 76.4; H, 6.3.

1-Keto-2-methyl-2-carbomethoxy-9-ethyl-1,2,3,4-tetrahydrophenanthrene. The 1-keto-2-

carbomethoxy-9-ethyl derivative (1.23 g.) was converted by treatment of the sodio salt with methyl iodide by the procedure described for an analogous compound (8) to the corresponding 2-methyl derivative; yield 1.05 g. (81.5%) of colorless needles, m.p. 111–112°. An alcoholic solution of the product gave no color with ferric chloride.

Anal. Calc'd for $C_{17}H_{18}O$: C, 77.0; H, 6.8.

Found: C, 77.4; H, 6.8.

1-Keto-2-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene (IId). 1-Keto-2-methyl-2-carbomethoxy-9-ethyltetrahydrophenanthrene (2.97 g.) was hydrolyzed and decarboxylated by refluxing with alcoholic potassium hydroxide (8) to give 2.08 g. (87%) of crude product (m.p. 52.5–54.5°) which crystallized from methanol as tiny colorless needles; m.p. 55–56°.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.7; H, 7.6.

Found: C, 85.3; H, 7.7.

2-Methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene (Ib). (a) From 2-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. In the manner indicated for the reduction of 1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene, 17.6 g. (97.5%) of almost colorless liquid (b.p. 143–146° at 0.05 mm.) was obtained from 20 g. of the 2-methyl-9-acetyl compound.

The trinitrobenzene derivative crystallized from absolute alcohol in fine yellow needles; m.p. 102–103°.

Anal. Calc'd for $C_{21}H_{22}N_3O_6$: N, 9.6. Found: N, 9.4.

(b) From 1-keto-2-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene (IId). One and two-tenths grams of the ketone was converted to the 2-methyl-9-ethyltetrahydrophenanthrene by reduction as previously indicated (6). The trinitrobenzene derivative was identical with that obtained in (a).

Treatment of a sample of the above hydrocarbon with palladium-charcoal catalyst (7) as described for the preparation of 2-methylphenanthrene from the corresponding tetrahydro compound yielded 2-methyl-9-ethylphenanthrene as a colorless liquid; b.p. 143–146° at 0.05 mm.

The trinitrobenzene derivative prepared in absolute ethanol melted at 129–130°.

Anal. Calc'd for $C_{21}H_{22}N_3O_6$: N, 9.7. Found: N, 9.6.

2-Methyl-9-bromoacetyl-1,2,3,4-tetrahydrophenanthrene (Ic). To a solution of 20 g. of 2-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene in 800 ml. of absolute ether cooled to 5–10° was added 14 g. of bromine dropwise with stirring. After the mixture had come to room temperature, it was cooled, and the crystalline product collected by filtration and washed with dry ether; yield 11.95 g. (45%), m.p. 114–115.5°. The second and third crops, obtained from the filtrate by concentration in the cold, after washing with 5% sodium bicarbonate, water, and drying, amounted to 10.79 g. after recrystallization from 30–60° petroleum ether-acetone, and brought the total yield to 22.69 g. (85%). Further recrystallization of a sample from the same solvent gave colorless needles; m.p. 116–117°.

Anal. Calc'd for $C_{17}H_{17}BrO$: C, 64.4; H, 5.4; Br, 25.2.

Found: C, 64.4; H, 5.6; Br, 25.1.

2-Methyl-1,2,3,4-tetrahydro-9-phenanthroic acid (Id). By the hypochlorite procedure of Newman and Holmes (9), 2 g. of the 9-acetyl derivative was oxidized to the 9-carboxylic acid; yield 2 g. (99%), m.p. 195–198°. Recrystallization from acetone gave colorless prisms which melted at 207–208°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7.

Found: C, 80.0; H, 70.0.

2-Methyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid (If). By the Willgerodt reaction as employed by Fieser and Kilmer (10) and modified by Bachmann and Cronyn (2), 1.3 g. (61%) of 2-methyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid amide (Ie) melting at 219–225° was obtained from 2 g. of the 2-methyl-9-acetyltetrahydrophenanthrene. Recrystallization from acetone gave 1.07 g. (50%) of glistening leaflets; m.p. 235–236°.

Anal. Calc'd for $C_{17}H_{18}NO$: N, 5.5. Found: N, 5.4.

A mixture of 0.79 of the above amide, 15 ml. of glacial acetic acid, 7 ml. of hydrochloric acid, and 1.5 ml. of water was refluxed for twenty-four hours and then poured while hot

into 40 ml. of hydrochloric acid. The colorless needles of (If) which separated on cooling were washed with dilute acetic acid and water; yield 0.79 g., m.p. 171–172.5°. Several recrystallizations from ethyl acetate raised the melting point to 176–177°.

Anal. Calc'd for $C_{17}H_{13}O_2$: C, 80.3; H, 7.1.

Found: C, 80.1; H, 7.2.

2-Methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene oxime. A mixture of 23.8 g. of 2-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene, 20.8 g. of hydroxylamine hydrochloride, 90 ml. of absolute alcohol, and 30 ml. of pyridine was refluxed for four hours on a steam-bath. Most of the alcohol was distilled, the residue was stirred with cold water until the product solidified, and the oxime was recrystallized from ethanol; yield 23 g. (91%), m.p. 176–182°. After four recrystallizations from ethanol a sample formed colorless prisms; m.p. 183–183.5°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.4.

2-Methyl-9-acetyl-amino-1,2,3,4-tetrahydrophenanthrene (Ig). A mixture of 23 g. of the aforementioned oxime (once recrystallized) and 18.9 g. of phosphorus pentachloride in 420 ml. of dry benzene was refluxed for fifteen minutes, poured into an equal volume of cold water, and stirred vigorously for three hours while the product precipitated. After twelve hours, the crude product was separated by filtration, taken up in hot ethanol-methanol, and the solution treated with Norit. The first and second crops totaled 17.8 g. (77.5%) of fluffy colorless needles; m.p. 175–176°. A sample after two recrystallizations melted at 180–181°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.5.

2-Methyl-9-amino-1,2,3,4-tetrahydrophenanthrene (Ih). A solution of 10.12 g. of the 2-methyl-9-acetyl-amino derivative (as obtained from the first crystallization) in 400 ml. of alcohol and 22 ml. of hydrochloric acid was refluxed for twenty-four hours on a steam-bath. The alcohol was evaporated under reduced pressure, the residual amine hydrochloride was dissolved in four liters of boiling water, and the solution was treated with a small amount of Norit and filtered into a flask immersed in an ice-bath. Slow addition of aqueous ammonia to the stirred solution precipitated the amine, which was filtered and dried overnight in a vacuum desiccator protected from light. The white powder, 8.5 g. (100%), m.p. 88.5–90°, was sufficiently pure for subsequent reactions. It became discolored upon exposure to air and light or when heated in solution. Evaporative distillation of a sample at 0.05 mm. yielded colorless needles; m.p. 90–91°.

Anal. Calc'd for $C_{16}H_{17}N$: N, 6.6. Found: N, 6.5.

The *amine hydrochloride*, prepared by dissolving a sample of the evaporatively distilled amine in hot dilute hydrochloric acid and cooling in the dark in an atmosphere of carbon dioxide, after drying *in vacuo* and sublimation at 0.05 mm., formed colorless needles; m.p. 255–256°.

Anal. Calc'd for $C_{16}H_{18}ClN$: Cl, 14.3. Found: Cl, 14.2.

The *picrate* crystallized from absolute alcohol in golden needles; m.p. 188–189° dec. with previous sintering at 185°.

Anal. Calc'd for $C_{21}H_{20}N_4O_7$: N, 12.7. Found: N, 12.4.

Acetylation of 2-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene. By the method described for the preparation of 2-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene, from 16.2 g. 2-methyl-9-ethyltetrahydrophenanthrene and 11.4 g. of acetyl chloride was obtained 15.7 g. (81.5%) of a product which was probably *2-methyl-7-acetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene*; m.p. 72–75°. Recrystallization from ethanol gave 13.2 g. (68.5%) of colorless prisms; m.p. 77–78°.

Anal. Calc'd for $C_{19}H_{22}O$: C, 85.7; H, 8.3. Found: C, 85.3; H, 8.3.

Bromination of the above acetyl compound (12 g.) in the manner described for the analogous 2-methyl-9-bromoacetyl compound gave a total yield of 13.7 g. (97%) of the bromoacetyl derivative which was probably *2-methyl-7-bromoacetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene*; m.p. 102–103°. A sample crystallized from ethanol in fine, colorless needles; m.p. 104–105°.

Anal. Calc'd for $C_{18}H_{17}BrO$: C, 66.2; H, 6.1; Br, 23.2. Found: C, 66.4; H, 6.1; Br, 23.1.

1-Keto-9-ethyl-1,2,3,4-tetrahydrophenanthrene oxime. A mixture of 13.2 g. of 1-keto-9-ethyltetrahydrophenanthrene (6), 12.3 g. of hydroxylamine hydrochloride, 53 ml. of absolute alcohol, and 17.7 ml. of pyridine was refluxed for four hours, the alcohol was removed and water added. The solid product (13.9 g.; 98.5%) crystallized from alcohol in colorless platelets; m.p. 152–153.5°. Several further recrystallizations of a sample raised the melting point to 156–157°.

Anal. Calc'd for $C_{18}H_{17}NO$: N, 5.9. Found: N, 5.2.

1-Amino-9-ethyl-1,2,3,4-tetrahydrophenanthrene. A solution of 11.4 g. of the aforementioned oxime (once recrystallized) in 140 ml. of ethanol reduced with 2% sodium amalgam by the method of Bachmann (11) gave 9.2 g. (87%) of the amine as a colorless oil; b.p. 168–173° at 0.05 mm.

The *picrate* crystallized from absolute alcohol in yellow prisms; m.p. 212–213° dec.

Anal. Calc'd for $C_{22}H_{23}N_4O_7$: N, 12.3. Found: N, 12.4.

SUMMARY

2-Methyl-1,2,3,4-tetrahydrophenanthrene and 2-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene have been synthesized, the latter by two methods. Various new derivatives of these hydrocarbons and of 9-ethyl-1,2,3,4-tetrahydrophenanthrene have been prepared.

ANN ARBOR, MICHIGAN

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SYNTHESIS OF *p*-ALKYLSTYRENES

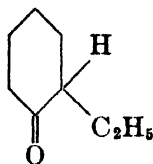
M. SULZBACHER AND E. BERGMANN

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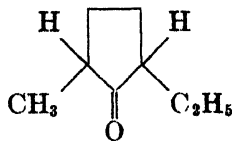
Recently, a number of nuclear-substituted styrenes have been synthesized and their polymerization investigated (1-7). It might, therefore, be useful to report on the synthesis of a number of *p*-alkylstyrenes which has been carried out in order to obtain oil-soluble polystyrenes. Polystyrene itself is insoluble in mineral oils (*e.g.* hydraulic oils), but the introduction of alkyl groups in the *p*-position increases the oil solubility gradually with increasing length of the alkyl chain. The polymers of *p*-heptyl- and *p*-(2-ethylhexyl)styrene are easily soluble in mineral oils.

For the synthesis of the *p*-alkylstyrenes the corresponding *p*-alkylacetophenones were reduced with aluminum isopropoxide, and the (*p*-alkylphenyl)-methylcarbinols formed dehydrated with potassium hydrogen sulfate *in vacuo*, according to the method of Brooks (3). *p*-Methyl-, *p*-ethyl-, *p*-butyl-, *p*-heptyl- and *p*-(2-ethylhexyl)-styrene were thus prepared.

For the synthesis of heptylbenzene (from which *p*-heptylacetophenone was obtained in the usual way), Clemmensen's method of reduction was applied successfully to heptanoylbenzene. (2-Ethylhexyl)benzene could not be prepared equally well through (2-ethylhexanoyl)benzene. In the synthesis of the latter ketone a noteworthy side-reaction was observed, *viz.* the formation of a ketone $C_8H_{16}O$ by intramolecular dehydrohalogenation. Formally, this ketone could be 2-ethylcyclohexanone (I) or 2-ethyl-5-methylcyclopentanone (II).



I



II

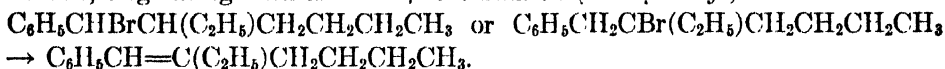
Although no conclusive evidence is offered for either of the two formulas, formula (II) is preferred, as the steric encumbrment of the carbonyl group may explain its resistance to semicarbazone formation and its slackness in the reaction with phenylmagnesium bromide.

This is undoubtedly an unexpected reaction, although the acylation of paraffinic chains by acyl chlorides in the presence of aluminum chloride has been observed before (8).

(2-Ethylhexyl)benzene was, therefore, prepared from 2-ethylhexanol and benzene with aluminum chloride.

In the study of the synthetic methods available in this series, an attempt was also made to prepare β -(*p*-heptylphenyl)ethyl chloride by interaction of β -chloroethyl *p*-toluenesulfonate (9) and the magnesium derivative of *p*-heptylbromo-

benzene. The latter substance proved available by condensation of heptanoyl chloride and bromobenzene and Clemmensen reduction of the *p*-heptanoyl-bromobenzene so obtained. Its Grignard derivative, however, gave very unsatisfactory yields of the desired β -phenylethyl chloride derivative. In the 2-ethylhexyl series the Friedel-Crafts reaction of 2-ethylhexanoyl chloride with bromobenzene proved unsatisfactory, as partial debromination and formation of resins took place (10). The peculiar reactivity of the 2-ethylhexyl group expresses itself also in the following fact: Bromination of (2-ethylhexyl)benzene in carbon tetrachloride solution at low temperature gave a product which decomposed with evolution of hydrogen bromide when distilled *in vacuo*. The compound formed was an unsaturated hydrocarbon, probably 1-phenyl-2-ethyl-1-hexene, originating from an α - or β -brominated (2-ethylhexyl)benzene:



EXPERIMENTAL

p-Methyl-, *p*-ethyl-, and *p*-butyl-acetophenone were prepared from the alkylbenzenes and acetic anhydride in the presence of aluminum chloride (11, 12). The yields were above 85% of theory; *p*-ethylacetophenone boiled at 130°/23 mm. (13), the butyl compound at 167°/33 mm. (12c, 14) [lit. (13a) 100–103°/3 mm.; (14a) 140–141°/21 mm.].

Heptanoic acid. The catalytic oxidation of heptanal described by Weizmann (15) is preferably carried out using pure oxygen; the reaction is exothermic and raises the temperature from 20° to 65°. After 8 hours, 3.7% of the initial heptanal was recovered; heptanoic acid was obtained in 94.5% yields (or 98.2%, taking into account the recovered aldehyde); b. p. 106–110°/9 mm.

Heptanoyl chloride. The slow addition of 851 g. (7.2 moles) of freshly distilled thionyl chloride to 845 g. (6.5 moles) of heptanoic acid, followed by heating at 50° for 8 hours and at 100° for one hour, and then distilling, gave 840 g. (87.0%) of heptanoyl chloride; b.p. 91–93°/35 mm.

The small excess of thionyl chloride was recovered by distillation at ordinary pressure and the residue purified by vacuum distillation; b.p. 91–93°/35 mm.; yield, 840 g. (87.0%).

Heptanoylbenzene. A suspension of 750 g. (5.6 moles) of powdered anhydrous aluminum chloride in 4 liters of dry benzene was well stirred and cooled in ice-water. Eight hundred thirty-two grams (5.6 moles) of *n*-heptanoyl chloride was added slowly during several hours, at less than 10°. The mixture was allowed to stand for twelve hours at room temperature, gently refluxed during three hours, and decomposed with ice and concentrated hydrochloric acid; b.p. 138–139°/14 mm.; yield, 905 g. (85.0%). The substance solidified at about 10°.

Anal. Calc'd for $\text{C}_{13}\text{H}_{20}\text{O}$: C, 82.1; H, 9.5.

Found: C, 82.5; H, 9.1.

Heptylbenzene. Heptanoylbenzene (190 g.; 1 mole) was reduced with amalgamated zinc wool (400 g.) and hydrochloric acid (400 cc. of concentrated acid and 300 cc. of water), more concentrated acid being added from time to time to the boiling mixture, until all the metal had disappeared. The oily layer and the ethereal extract of the water layer were subjected to fractional distillation; b.p. 110°/11 mm.; yield, 124 g. (70.5%). Nineteen grams of unchanged heptanoylbenzene was recovered.

Anal. Calc'd for $\text{C}_{13}\text{H}_{20}$: C, 88.6; H, 11.4; mol. wt., 176.

Found: C, 88.3; H, 11.2; mol. wt., 179.

p-Heptylacetophenone. To a well-agitated solution of 176 g. (1 mole) of heptylbenzene in 450 cc. of carbon disulfide, 300 g. (2.24 moles) of powdered aluminum chloride was added slowly. The mixture was heated to the boiling point, and 91.8 g. (0.9 mole) of acetic an-

hydride was added within one hour. After a further hour, the reaction product was treated with ice and concentrated hydrochloric acid and extracted with benzene. After washing with water, dilute sodium hydroxide solution and again water, and drying, the solution was distilled; b.p. 165–175°/10 mm. [lit. (14a) b.p. 176–179°/13 mm.]; yield, 98 g. (45.0%). It is assumed by analogy that acetylation takes place in the *p*-position to the heptyl group.

Anal. Calc'd for $C_{18}H_{22}O$: C, 82.5; H, 10.1.

Found: C, 82.7; H, 10.1.

A higher-boiling fraction (198–204°/10 mm.) was obtained, probably a diacetylheptylbenzene. A small quantity of acetophenone was also present in the head fractions, due to a degrading action of aluminum chloride on *p*-heptylacetophenone.

(2-Ethylhexyl)benzene. (a) When 65 g. (0.5 mole) of 2-ethylhexanol, 67 g. (0.5 mole) of powdered aluminum chloride and 312 g. (4 moles) of benzene were mixed at room temperature, no appreciable reaction took place. The mixture was refluxed for six hours, decomposed with ice and concentrated hydrochloric acid, and the organic layer dried and freed from the excess benzene. (2-Ethylhexyl)benzene boiled at 129–131°/15 mm.; yield, 47.2 g. (50.0%, calculated on the 2-ethylhexanol used). A higher-boiling fraction, amounting to 10 g., was also obtained, boiling under the same pressure at 145–210°, and consisting of di- and possibly tri-octylbenzenes. Hardly any resinous residue remained in the distillation flask. Almost the total balance of unchanged 2-ethylhexanol was recovered as head fraction in the distillation.

Anal. Calc'd for $C_{14}H_{22}$: C, 88.3; H, 11.7.

Found: C, 88.0; H, 11.5.

(b) When the quantity of aluminum chloride was doubled, the reaction began at room temperature, and the octyl alcohol had to be added slowly, the temperature being kept below 10°. The reaction was again completed by refluxing for six hours. Treatment as above showed a slight reduction in the yield of (2-ethylhexyl)benzene (40 g. instead of 47.2 g.), an increase in the fraction consisting of di- and tri-octylbenzenes (14 g. instead of 10 g.) and in the formation of a substantial amount (20 g.) of resinous residue with a corresponding loss of recoverable 2-ethylhexanol.

(c) The reaction between benzene and 2-ethylhexyl bromide gave poor results; the yield of (2-ethylhexyl)benzene was 10%, that of the di- and tri-octylbenzene fraction 20%.

p-(2-Ethylhexyl)acetophenone was prepared from the foregoing hydrocarbon (175 g.) and acetic anhydride (75.2 g.) in carbon disulfide (400 cc.) and in the presence of aluminum chloride (275 g.) in the manner described for *p*-heptylacetophenone. Fractional distillation of the reaction product gave 32 g. of acetophenone, b.p. 92–94°/18 mm., and 85 g. (40%) of the desired ketone, b.p. 189°/17 mm.

Anal. Calc'd for $C_{16}H_{24}O$: C, 82.8; H, 10.3.

Found: C, 83.1; H, 10.1.

It should be borne in mind that both in the condensation of 2-ethylhexanol with benzene and in that of (2-ethylhexyl)benzene with acetic anhydride, the aluminum chloride may cause isomerization of the aliphatic chain. This aspect of the synthesis described here, has not been investigated.

(*p*-Alkylphenyl)methylcarbinols. The reduction of the *p*-alkylacetophenones (1 mole) was carried out with one mole of aluminum isopropoxide in 800 cc. of isopropyl alcohol with continuous removal of the acetone formed and occasional replacement of the part of the liquid which had distilled off. When no more acetone could be detected in the distillate, the reaction mixture was either directly treated with 20% aqueous potassium hydroxide or freed from excess solvent *in vacuo* and poured into ice-cold dilute hydrochloric acid. Extraction with ether, neutralization, drying of the extract, and distillation gave the desired carbinols (Table I).

p-Alkylstyrenes. Using the method of Brooks (3), the (*p*-alkylphenyl)methylcarbinols were heated under 100 mm. pressure with 1% by weight of potassium hydrogen sulfate and a nearly equal amount of hydroquinone in a Claisen flask. The distillate was dissolved in ether, dried, and fractionated (Table II).

4-Heptanoylbromobenzene. At 0°, 58 g. of heptanoyl chloride was added slowly to a well-agitated suspension of 106 g. of powdered aluminum chloride in 350 cc. of carbon disulfide and 46 cc. of bromobenzene. The mixture was then kept for twelve hours at room temperature, refluxed for two hours and decomposed with ice and concentrated hydrochloric acid. Fractionation under 30 mm. pressure gave: (a) at 145–150°, 19 g. of heptanoylbenzene (corresponding to 25% of the chloride employed); (b) at 225–230°, 42 g. of 4-heptanoylbromobenzene (corresponding to 39% of the acid chloride employed).

The second fraction crystallized and was triturated with petroleum ether; from isopropyl alcohol shiny leaflets, m.p. 81°.

TABLE I
(*p*-ALKYLPHENYL)METHYLCARBINOLS $\text{RC}_6\text{H}_4\text{CHOHCH}_3$

R =	% YIELD FROM $\text{RC}_6\text{H}_4\text{COCH}_3$	B. P. °C/MM.	CALC'D C	CALC'D H	FOUND C	FOUND H
Methyl ^a	70.0	120/19				
Ethyl ^a	87.3	120/14				
Butyl	88.0	149–153/30	80.9	10.2	81.4	10.1
Heptyl	69.1	180–182/15	81.8	11.0	82.2	10.9
2-Ethylhexyl	64.4	170–174/18	82.1	11.0	83.0	11.0 ^b

^a Described without physical constants by Gauthier and Gauthier (16).

^b The product contained a small amount of (*p*-ethylhexyl)styrene.

TABLE II
p-ALKYLSTYRENES, $\text{RC}_6\text{H}_4\text{CH}=\text{CH}_2$

R =	% YIELD FROM $\text{RC}_6\text{H}_4\text{CHOHCH}_3$	B. P. °C/MM.	CALC'D C	CALC'D H	FOUND C	FOUND H
Methyl ^a	71.8	63/15	91.5	8.5	91.3	8.3
Ethyl ^b	72.0	86/20	90.9	9.1	90.5	9.0
Butyl	70.0	116–118/15	90.0	10.0	89.7	10.2
Heptyl	69.3	155–156/12	89.1	10.9	88.9	10.9
2-Ethylhexyl	30.0	138–141/7	88.9	11.1	88.7	11.3

^a Shoruigin and Shoruigina (17a) b.p. 51°/10 mm. Gauthier and Gauthier (16) b.p. 166–167°/724 mm. Cf. Palmer (17b) and Matui (17c).

^b Gauthier and Gauthier (16) b.p. 86°/20 mm. Matui (18a) b.p. 175–177°. Cf. (18b).

4-Heptylbromobenzene. The reduction of 40 g. of the foregoing ketone was carried out with 60 g. of amalgamated zinc wool, 50 cc. of toluene, 35 cc. of water and 90 cc. of concentrated hydrochloric acid. 4-Heptylbromobenzene boiled at 154–157°/10 mm.; 187–190°/35 mm.; yield, 30 g. (80%).

Anal. Calc'd for $\text{C}_{13}\text{H}_{18}\text{Br}$: C, 61.2; H, 7.5.

Found: C, 61.3; H, 7.4.

β -(4-Heptylphenyl)ethyl chloride. When 37 g. of 4-heptylbromobenzene was added to an ethereal suspension of 3.4 g. of magnesium, which had been activated with a few drops of methyl iodide, the reaction proceeded steadily; it was completed by boiling for two hours. Thirty-two grams of β -chloroethyl *p*-toluenesulfonate was then added. After twelve hours' standing, the solid cake was refluxed for six hours and decomposed with ice and dilute sulfuric acid. Fractionation gave two volatile products and a not inconsiderable quantity of resin: (a) b.p. 109°/10 mm.; heptylbenzene; yield, 10 g.; (b) b.p. 168°/10 mm.; β -(4-heptylphenyl)ethyl chloride; yield, 10 g. (30%).

Anal. Calc'd for $C_{15}H_{25}Cl$: C, 75.6; H, 9.4; Cl, 15.0; mol. wt. 238.

Found: C, 75.4; H, 9.8; Cl, 14.6; mol. wt. 216.

2-Ethylhexanoylchloride. 2-Ethylhexanoic acid (13) (120 g.) was refluxed with thionyl chloride (200 cc.) for six hours after the spontaneous reaction had subsided; b.p. 114–116°/75 mm.; 101°/40 mm.; yield, quantitative.

Anal. Calc'd for $C_{12}H_{22}ClO$: C, 59.3; H, 9.3.

Found: C, 59.0; H, 9.1.

(2-Ethylhexanoyl)benzene. The mixture of 109 g. of 2-ethylhexanoyl chloride, 100 g. of aluminum chloride and 700 cc. of benzene, prepared at 0°, was kept at room temperature for two days, refluxed for two hours and decomposed with ice and concentrated hydrochloric acid. Fractional distillation gave (a) 41 g. of b.p. 149–150°/35 mm.; (b) 18 g. of b.p. 184–185°/45 mm. Fraction (a) had the formula $C_{14}H_{24}O$ and the structure (I) or (II). It did not form a semicarbazone, but reacted with phenylmagnesium bromide.

Anal. Calc'd for $C_{14}H_{24}O$: C, 76.2; H, 11.1.

Found: C, 76.3; H, 11.3.

Fraction (b) was the desired ketone; yield, 13%.

Anal. Calc'd for $C_{14}H_{20}O$: C, 82.4; H, 9.8.

Found: C, 82.6; H, 9.6.

When 21 g. of 2-ethylhexanoyl chloride reacted with 24 g. of bromobenzene in 150 cc. of carbon disulfide and in the presence of 37 g. of aluminum chloride, a considerable amount of resin formed. Fractional distillation gave 4 g. of the ketone $C_{14}H_{20}O$ (b.p. 149–150°/35 mm.), 4 g. of (2-ethylhexanoyl)benzene (b.p. 174–175°/35 mm.) and 3 g. (8%) of *p*-(2-ethylhexanoyl)bromobenzene (b.p. 210°/45 mm.).

1-Phenyl-2-methyl-5-ethylcyclopentanol. The interaction of 30 g. of the ketone $C_{14}H_{20}O$ and phenylmagnesium bromide (from 9 g. of magnesium and 56.3 g. of bromobenzene) was achieved by refluxing for two hours. Decomposition gave 16 g. of unchanged ketone (b.p. 149–150°/35 mm.; 53%) and 18 g. of the carbinol, b.p. 235–240°/50 mm. (yield, 37%).

Anal. Calc'd for $C_{14}H_{20}O$: C, 82.4; H, 10.0.

Found: C, 82.1; H, 9.9.

Bromination of (2-ethylhexyl)benzene. To a solution of 38 g. of (2-ethylhexyl)benzene in 100 cc. of carbon tetrachloride, 11 cc. of bromine was slowly added at a temperature not exceeding 5°. The reaction was rather violent. After twelve hours at room temperature, the reaction product was washed with sodium carbonate solution, dried with calcium chloride and distilled, first at ordinary pressure (carbon tetrachloride), then *in vacuo*. Practically all the product boiled under 20 mm. pressure at 135–140°, continuously giving off HBr. A small amount of a bromo compound, boiling at 212–214°/20 mm. was also obtained, but on redistillation it decomposed, too, into hydrogen bromide and the product boiling at 135–140°. The latter was treated with solid potassium hydroxide, filtered and redistilled; yield, 34 g. It was an unsaturated hydrocarbon, presumed to be 1-phenyl-2-ethylhexene-(1).

Anal. Calc'd for $C_{14}H_{20}$: C, 89.4; H, 10.6.

Found: C, 89.4; H, 10.7.

LONDON, ENGLAND

REHOVOTH, PALESTINE

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THE SYNTHESIS AND PROPERTIES OF DI-2,4-DIMETHYLPHENYLTHIOCARBAZONE

RALPH E. OESPER AND JOSEPH J. KLINGENBERG

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The superiority of di-*beta*-naphthylthiocarbazone over diphenylthiocarbazone (dithizone) as a reagent in the determination of mercury and zinc is now well

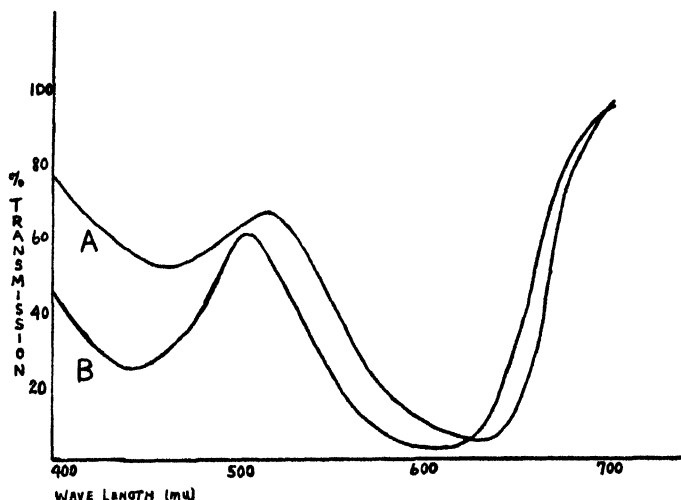


FIG. 1

A—Di-2,4-dimethylphenylthiocarbazone 7.5 micrograms/ml. CHCl_3 .B—Dithizone 10.0 micrograms/ml. CHCl_3 .

Cell length—0.1 cm.

TABLE I
COLOR COMPARISON OF THE VARIOUS METAL THIOCARBAZONATES
THIOCARBAZONE

COLOR OF	DIPHENYL-(DITHIZONE)	DI-2,4-DIMETHYLPHENYL-	DI- <i>beta</i> -NAPHTHYL-
CHCl_3 soln. ^a	green	green-blue	blue-green
Hg Complex ^b	amber	orange	pink
Cd Complex	cherry red	red	violet
Zn Complex	pink	violet	violet
Bi Complex	orange	purple	magenta
Ag Complex	yellow	orange	—

^a Concentration of CHCl_3 solutions 0.001%.^b 10–20 micrograms of metal ions was used.

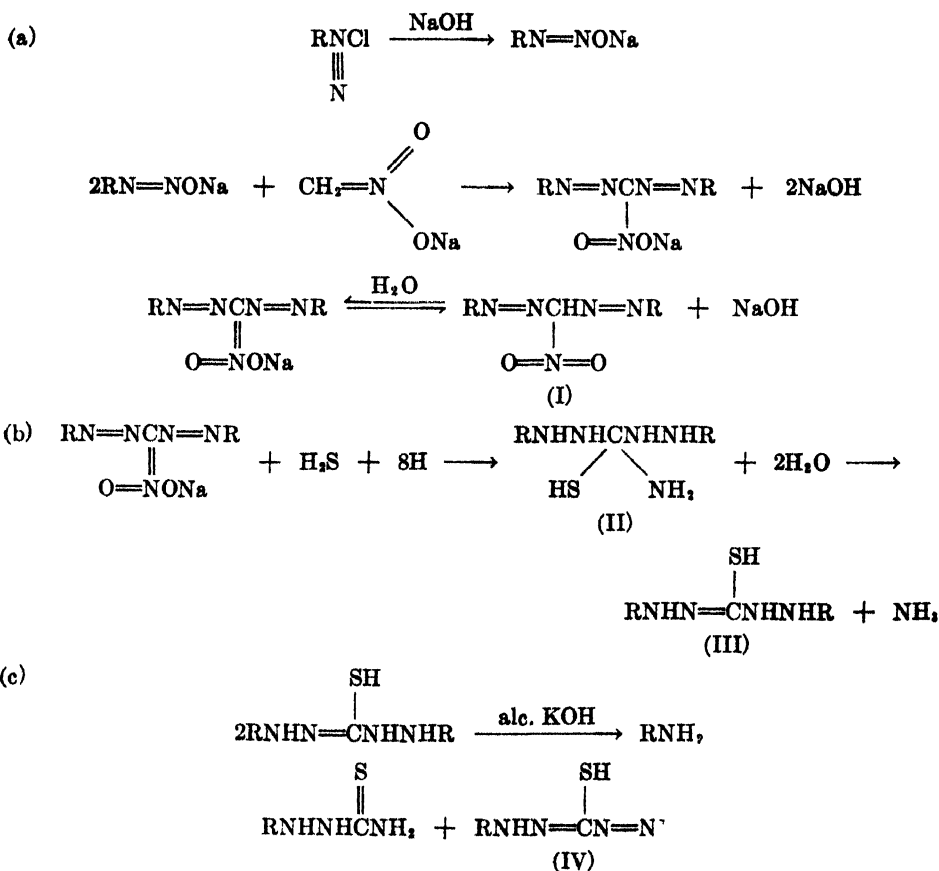
established (1, 2). Since the improvement clearly is due to the weighting effect resulting from the substitution of phenyl by naphthyl, it seemed likely that similar advantages might be secured by replacing the phenyl groups with substituted phenyl groups. Accordingly, in the present study, di-2,4-dimethylphenylthiocarbazone was synthesized and its analytical behavior explored.

As expected, the properties of this new reagent lie between those of dithizone and di-*beta*-naphthylthiocarbazone. The transmittancy curve (Figure 1) is similar to that of dithizone but is slightly displaced toward longer wave lengths. The colors of its metal complexes are intermediate between those of the corresponding diphenyl- and dinaphthyl- thiocarbazonates (see Table I).

The shade and intensity of its metal derivatives present no inducement for introducing the new compound into analytical practise. However, the experimental confirmation of its predicted properties and the experience gained in its preparation justify the publication of the results of this investigation, since the findings may be of value in future studies of this group of extremely useful reagents.

The compound was prepared by a procedure that approximates the method used by Hubbard (3) to produce the di-*beta*-naphthyl derivative. Careful attention to purity of reagents and close maintenance of the prescribed conditions are essential to success in producing any of the thiocarbazonates in satisfactory yield and purity.

The synthesis involves three steps: namely, production of (a) the nitroformazyl compound; (b) the thiocarbazide; (c) the thiocarbazone. These steps can be represented:



EXPERIMENTAL

(a). *The nitroformazyl compound.* Four and eight-tenths ml. of sodium hydroxide solution (25 g./100 ml.) is diluted with 18.5 ml. of absolute alcohol and 1.6 ml. (0.03 mole) of freshly distilled nitromethane added. The mixture is cooled to -5° and the crystals which separate are dissolved by adding 100 ml. of ice-water. The solution of alkaline nitromethane is kept at -5° until used.

2,4-Dimethylaniline, 7.25 g. (0.06 mole), is rapidly mixed with 15 ml. of hydrochloric acid (sp. gr. 1.18) and 25 ml. water. The solid mass of hydrochloride crystals is cooled to 0° , and slowly diazotized (vigorous stirring) by the addition of 5 g. of sodium nitrite dissolved in 10 to 15 ml. of water. The resulting amber solution (filtered if necessary) is transferred to a 250-ml. beaker, immersed in acetone, and cooled by addition of Dry Ice to this acetone bath. If desired, Dry Ice can be added directly to the diazotized solution. The latter is cooled to -10° , and then 40 ml. of sodium acetate solution (40 g. NaOAc·3H₂O/100 ml. solution) is added dropwise (mechanical stirring). The mixture is kept at -5° .

The alkaline nitromethane solution is now treated with 4.8 ml. of the sodium hydroxide solution, placed in a separatory funnel containing cracked ice, and dropped slowly, with stirring, into the diazotized solution. The nitroformazyl compound (I) separates at once as an orange precipitate, which darkens somewhat on standing. The strong tendency to

TABLE II
PROPERTIES AND ANALYSES OF DI-2,4-DIMETHYLPHENYLTHIOCARBAZONE
AND INTERMEDIATES

	COLOR	MELTING POINT $^{\circ}$ C.	ANALYSES
Nitroformazyl	red	145-148	Nitrogen Calc'd 21.37 Found 21.40
Thiocarbazide	yellow	168-171	—
Thiocarbazone	blue-black	152-154	Sulfur Calc'd 10.26 Found 10.50

form tar is minimized by keeping the temperature low, by waiting long enough for the nitrogen oxides to escape after diazotization, and by employing pure nitromethane. After 30 minutes, the precipitate is filtered with suction and washed thoroughly with ice-water. (If the product is tarry the filtration is slow and the washing with water may be omitted.) The precipitate is transferred to a beaker, stirred with 50 ml. of 50% acetic acid, filtered with suction and washed, first with 10% acetic acid and then with water. The air-dried product is boiled with 150 ml. of absolute alcohol. The bright red residue is washed with 10 ml. of hot alcohol and dried. The average yield from 7.25 g. of 2,4-dimethylaniline is 2 g. of the nitroformazyl compound. Larger proportions may be used to carry out the reaction if desired.

(b). *The thiocarbazide.* Ten g. of the product from (a) is placed in a wide mouth bottle with 100 ml. of absolute alcohol. Dry ammonia gas is passed through the cooled suspension for 15 to 25 minutes. Hydrogen sulfide is then passed into the suspension (mechanical stirring if desired). Visible reduction starts in about 30 minutes and then proceeds quickly. The end of the reaction is signalled by the disappearance of the red formazyl compound and the deposition of light yellow crystals (II). The contents of the flask are then treated with an equal volume of water to produce the thiocarbazide (III) which is filtered off. More water is sometimes necessary to complete the precipitation, as the product is fairly soluble in alcohol.

(c). *The thiocarbazone.* The unstable thiocarbazide compound is oxidized at once to the thiocarbazone by the addition of 20 ml. of 5% alcoholic potassium hydroxide. A clear

dark red solution forms. It is drained off and neutralized by pouring into a liter of approximately 0.2 normal hydrochloric acid. The resulting blue-black precipitate is filtered off and air dried.

The method employed for purifying dithizone (4) cannot be used because di-2,4-dimethylphenylthiocarbazone, like the *beta*-naphthyl derivative, is insoluble in ammonia. The impure carbazone (IV) can be purified by dissolving it in chloroform, washing the solution with water, and then precipitating the product by adding absolute alcohol. An average yield of 0.3 g. of pure carbazone was obtained per gram of crude material purified.

Nitrogen analyses were carried out by the Dumas combustion method. Attempts to use the standard and modified Kjeldahl procedure were not successful as part of the nitrogen is lost. The thiocarbazide, because of its instability, was not analyzed. For analytical data and properties of the compounds prepared see Table II.

CINCINNATI 21, OHIO

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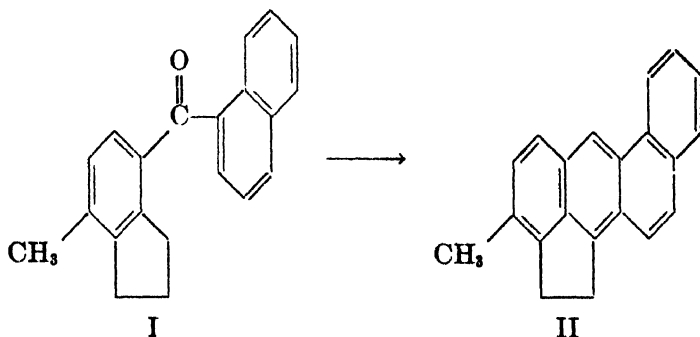
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THE SYNTHESIS OF 20-METHYLCHOLANTHRENE LABELED IN THE 11-POSITION WITH CARBON FOURTEEN¹

WILLIAM G. DAUBEN

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In connection with investigations (1) under way in this university concerning the distribution and the metabolism of carcinogenic hydrocarbons, it was desired to prepare 20-methylcholanthrene labeled with C¹⁴. All of the reported syntheses (2, 3, 4) of this carcinogen (II) make use of the Elbs reaction (5) on 4-(1-naphthyl)-7-methylhydrindene (I).



Three routes to this desired ketone have been described. The method of Fieser and Seligman (2), using 4-cyano-7-methylhydrindene and 1-naphthylmagnesium bromide, gives the ketone in 89% yield. Bachmann (4) has reported that this same ketone is obtained in only 49% yield when the Grignard reagent of 4-bromo-7-methylhydrindene is condensed with 1-naphthonitrile. From the viewpoint of a synthesis using C¹⁴, neither of these two methods is highly desirable, since the cyano compound must be prepared from sodium cyanide. The preparation of inorganic cyanide from barium carbonate, the form in which radioactive carbon is received at present, is known to be troublesome and erratic.²

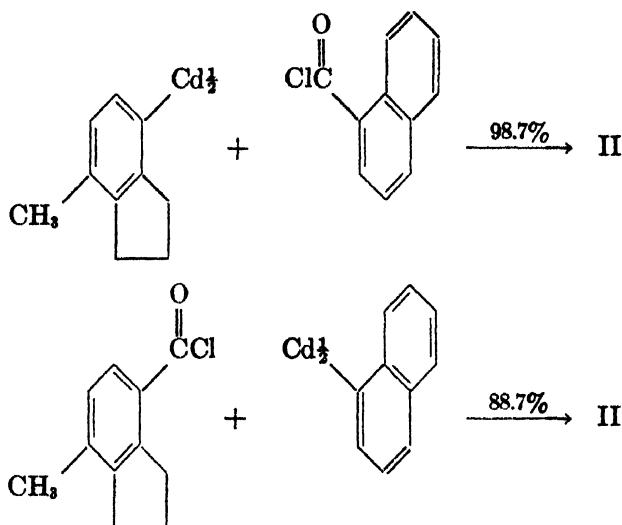
Fieser and Seligman (3) also have prepared the ketone in 45% yield by allowing 1-naphthoyl chloride to react with the Grignard reagent of 4-bromo-7-methylhydrindene. This method would be desirable since 1-naphthoic acid could easily be prepared by the carbonation of 1-naphthylmagnesium bromide with radioactive carbon dioxide. However, in view of low yield obtained in the above condensation, other methods of preparation of the desired ketone, employing the acid chloride, were investigated.

It was found that when 1-naphthoyl chloride was allowed to react with the cadmium derivative of 4-bromo-7-methylhydrindene, 4-(1-naphthoyl)-7-methyl-

¹ This work was supported in part by a grant from the University of California Cancer Fund.

² Since this work was completed, Loftfield (6) has reported that sodium cyanide can readily be prepared from barium carbonate in a yield of 96%.

hydrindene was isolated in 98.7% yield. When the acid chloride of 4-carboxy-7-methylhydrindene was allowed to react with *bis*-(1-naphthyl)cadmium, the ketone was obtained in 88.7% yield.



It is interesting to note that when the nitrile method is employed the yield varies from 48% to 89% depending on whether 4-cyano-7-methylhydrindene or 1-naphthonitrile is used. However, when the above cadmium method is employed, little difference in yield is found.

In order to evaluate more fully each of the above schemes, the two acids were prepared in the manner usually employed for carbonation with radioactive carbon (7). It was found that when 1-naphthylmagnesium bromide was carbonated, 1-naphthoic acid was formed in 82% yield. When the Grignard of 4-bromo-7-methylhydrindene was treated in similar manner, 4-carboxy-7-methylhydrindene was isolated in a yield of only 64%.

20-Methylcholanthrene-11-C¹⁴ (3-methylcholanthrene-6-C¹⁴) was prepared by the route employing 1-naphthoic acid. The over-all yield based on radioactive barium carbonate was 30.6%.

It is found that if the volatile by-products of the Elbs pyrolysis are burned, the carbon dioxide received is highly radioactive. A similar result was obtained in the preparation of radioactive 1,2,5,6-dibenzanthracene (1). Fieser has postulated (5) that in this reaction, the ketone suffers some cleavage by the water evolved, and perhaps the acid formed is subsequently decarboxylated. This might explain the presence of the radioactive carbon in the volatile gases. It was not determined, however, if the carbon dioxide was evolved from the reaction directly.

EXPERIMENTAL³

Carboxyl-labeled 1-naphthoic acid. 1-Naphthylmagnesium bromide was prepared in an all-glass apparatus in a nitrogen atmosphere from 0.75 g. (0.031 mole) of magnesium and

³ All melting points are uncorrected.

6.2 g. (0.03 mole) of 1-bromonaphthalene in a mixture of 50 cc. of anhydrous ether and 10 cc. of dry benzene. An aliquot of the solution was titrated and the concentration was found to be 0.0005 mole of Grignard reagent per cc. of solution.

A volume of 42 cc. (0.021 mole) of the Grignard solution was carbonated with carbon dioxide generated from 3.640 g. (0.0184 mole) of radioactive barium carbonate, following the procedure described in previous publications (1, 7). The barium carbonate contained approximately 4.4 millicuries of carbon fourteen. The reaction was conducted at 0°, and was processed in the usual manner. The acid was isolated by extraction with 100 cc. of 1 *N* sodium hydroxide and was recrystallized from 25 cc. of dry toluene (Norit). The acid melts from 162.5–163.5° and the yield was 2.596 g. (82.4%).

Carboxyl-labeled 1-naphthoyl chloride. The carboxyl-labeled 1-naphthoic acid, 2.480 g. (0.014 mole), was heated on a steam-bath for 2 hours with 10 cc. of purified thionyl chloride. The excess reagent was removed at reduced pressure and the residual acid chloride was dissolved in dry benzene and the benzene distilled. This process was repeated two times, and the acid chloride was finally dissolved in 10 cc. of benzene.

Carbonyl-labeled 4-(1-naphthoyl)-7-methylhydrindene. A mixture of 12.3 g. (0.058 mole) of 4-bromo-7-methylhydrindene, 1.46 g. (0.06 mole) of magnesium, and a few drops of ethyl iodide in 50 cc. of ether and 20 cc. of benzene was refluxed in a nitrogen atmosphere for 24 hours. The resulting Grignard reagent was converted into the dialkylcadmium compound with 6.4 g. (0.035 mole) of anhydrous cadmium chloride (8). After refluxing the mixture for 1 hour, the solvents were distilled and 25 cc. of benzene was added. A solution of the carboxyl-labeled 1-naphthoyl chloride prepared above was added to the refluxing suspension of the cadmium compound, and the resulting mixture was heated for 1 hour. The reaction mixture was decomposed with dilute hydrochloric acid and the mixture distilled with steam to remove the volatile neutral products and the benzene. The remaining aqueous suspension of the sirup was extracted with ether and the ethereal solution washed with water, 1 *N* sodium hydroxide, water, and dried. The product distills at 223–225° at 2 mm. and the yield was 4.063 g. (98.7% based on the acid).

20-Methylcholanthrene-11-C¹⁴. The Elbs reaction was run in a small distillation flask with a sealed-on receiver, and was heated in a salt-bath at 405–410°. Four and six-hundredths grams (0.0145 mole) of 4-(1-naphthoyl)-7-methylhydrindene was pyrolyzed for 40 minutes, the evolved gases were passed directly into a combustion furnace, and the entire system swept with nitrogen. A precipitate of 265 mg. of highly radioactive barium carbonate was collected from the combustion.

When the reaction was complete, glass wool was added, the top of the flask sealed, and the methylcholanthrene was distilled at 1 mm., bath temperature 350–400°. The yellow distillate was dissolved in 70 cc. of *n*-propanol and the solution was concentrated to a volume of 45 cc. The yellow precipitate was recrystallized from 50 cc. of *n*-propanol, m.p. 176.5–177.5°, yield 1.436 g. (37.8%). Thus the over-all yield of methylcholanthrene, based on barium carbonate, is 30.6%.

4-Carboxy-7-methylhydrindene. The Grignard reagent of 4-bromo-7-methylhydrindene (0.006 mole) was carbonated with 1.06 g. (0.005 mole) of non-radioactive barium carbonate following the procedure used above. The acid was isolated by extraction with 1 *N* sodium hydroxide and was recrystallized from 12 cc. of ethanol. The yield was 0.60 g. (64%), and the acid melts at 223–225°. Fieser and Seligman (3) report the m.p. 227–229° (corr.).

4-(1-Naphthoyl)-7-methylhydrindene. 1-Naphthylmagnesium bromide was prepared from 3.1 g. (0.015 mole) of 1-bromonaphthalene as described above. The Grignard reagent was converted to *bis*-(1-naphthyl)cadmium by heating for 2 hours in benzene with 1.47 g. (0.008 mole) of anhydrous cadmium chloride. The resulting dialkylcadmium compound was allowed to react with 0.6 g. (0.003 mole) of the acid chloride of 4-carboxy-7-methylhydrindene and the reaction mixture was processed as described above. The resulting ketone boils at 223–225° at 2 mm., and the yield was 0.780 g. (88.7%).

Radioactivity measurements. The measurement of radioactivity was carried out with a thin-mica-window Geiger-Mueller tube on a scale of 64 circuit with a geometry of 17.6 ± 2.5 disintegrations per count. The activity was determined with thin, uniform layers

of barium carbonate, according to the procedure described in earlier publications (7). The 20-methylcholanthrene-11-C¹⁴ has a specific activity of 150,000 cts/min/mg. barium carbonate, or 110,000 cts/min/mg. methylcholanthrene, or 0.88 microcurie/mg. methylcholanthrene.

ACKNOWLEDGMENT

The author wishes to acknowledge the assistance given by Miss Raylene Adams during the progress of this work.

SUMMARY

1. 20-Methylcholanthrene-11-C¹⁴ has been synthesized in 30.6% over-all yield based on barium carbonate.

2. It has been shown that the yield of 4-(1-naphthoyl)-7-methylhydrindene is approximately the same whether the cadmium derivative of 4-bromo-7-methylhydrindene is allowed to react with 1-naphthoyl chloride, or *bis*-(1-naphthyl)cadmium is allowed to react with the acid chloride of 4-carboxy-7-methylhydrindene.

3. It has been found that the volatile by-products of the Elbs reaction result largely from the carbonyl carbon of the pyrolyzed ketone.

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THE SYNTHESIS OF ALICYCLIC COMPOUNDS
RELATED TO THE STEROIDS¹W. E. BACHMANN AND ANDRE S. DREIDING²

Received December 31, 1947

The route from cyclohexanone to desoxyandrosterone has been outlined in a previous paper (1). The synthesis of 9-methyl-1-decalone described there has been improved and several new intermediates have been isolated. The unsaturated Reformatsky ester (I), prepared from 2-methyl-2-carbomethoxycyclohexanone and methyl γ -bromocrotonate, was not dehydrated by boiling acetic anhydride. Thionyl chloride, however, followed by alcoholic potassium hydroxide, yielded 2-methyl-2-carboxycyclohexylidenecrotonic acid (III). Its ultra-violet absorption spectrum (curve 1) with a maximum at 270 m μ ($\log \epsilon = 4.4$) indicated that the diene system was conjugated with the carboxyl group (2). Catalytic reduction of the diene acid gave γ -2-methyl-2-carboxycyclohexanebutyric acid (IV) which proved to be the *cis* form. The distilled unsaturated Reformatsky ester (I) absorbed one mole of hydrogen in a few minutes. Alkaline hydrolysis of the product afforded crystalline γ -2-methyl-2-carboxy-1-hydroxycyclohexanebutyric acid (V). The dimethyl ester of V was dehydrated and hydrolyzed by treatment with thionyl chloride and alcoholic potassium hydroxide. The product was catalytically hydrogenated to IV.

A 90% yield of *cis*-9-methyl-2-carbomethoxy-1-decalone was obtained from the dimethyl ester of IV by the Dieckmann method when the solvent was distilled from the mixture during the reaction. Hydrolysis and decarboxylation proceeded quantitatively to yield *cis*-9-methyl-1-decalone. The cyclic ketone was formed in 41% yield when IV was treated with boiling acetic anhydride and the product was pyrolyzed.

The formation of the dimethyl ester of IV from *cis*-2-methyl-2-carboxycyclohexaneacetic acid (m.p. 163–164°), whose configuration had been established recently,³ proved that IV had the *cis* configuration. The acetic acid side chain was lengthened by two successive Arndt-Eistert reactions, and the resulting dimethyl ester of IV was converted to *cis*-9-methyl-1-decalone. This synthesis furnishes confirmatory evidence for the previously assigned configurations of the 9-methyl-1-decalones.

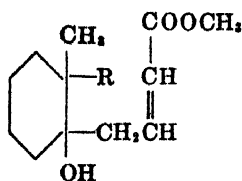
A new synthesis of γ -2-methyl- Δ^1 -cyclohexenebutyric acid consisted in condensing 2-methylcyclohexanone with methyl γ -bromocrotonate and zinc, hydro-

¹ Presented by W. E. Bachmann before the Chemical Societies in Basel, Zürich, and Geneva, Switzerland, May 8–16, 1947, under the auspices of the American-Swiss Foundation for Scientific Exchange.

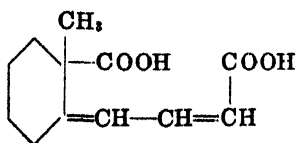
² From the Ph.D. dissertation of Andre S. Dreiding, 1947.

³ Davis, Ph.D. dissertation (1942) in "Summaries of Theses," Harvard Graduate School, 1946. The diacid (m.p. 158–163°) was synthesized by adding butadiene to citraconic anhydride, hydrogenating and hydrolyzing the product, and carrying out an Arndt-Eistert reaction on the secondary acid group.

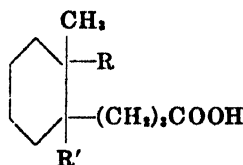
genating the unsaturated Reformatsky ester II, and dehydrating and hydrolyzing the product. The same acid was formed on pyrolysis of γ -2-methyl-2-carboxy-1-hydroxycyclohexanebutyric acid (V) at 200°. The unsaturated acid had been prepared previously by several methods, and its acid chloride had been cyclized by stannic chloride, and the product dehydrochlorinated to 9-methyl-1-octalone (Δ^6-10 or Δ^4-10) (3). We have now obtained the same ketone directly by cyclizing



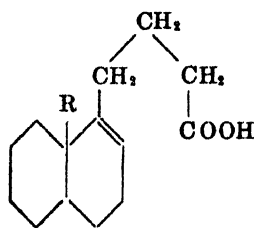
I, R = COOCH₃
II, R = H



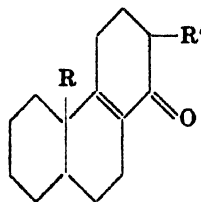
III



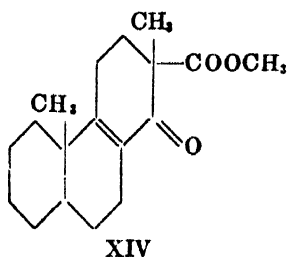
IV, R = COOH; R' = H
V, R = COOH; R' = OH
VI, R = H; R' = OH



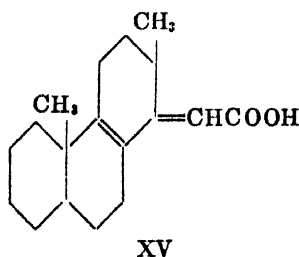
VII, R = CH₃
VIII, R = H



IX, R = CH₃; R' = H
X, R = R' = H
Xa, R' = H; aromatic A ring
XI, R = CH₃; R' = COCOOCH₃
XII, R = CH₃; R' = COOCH₃
XIII, R = R' = CH₃



XIV



XV

the unsaturated acid with a mixture of acetic anhydride and acetic acid containing a small amount of zinc chloride. The best results were obtained when the reaction was conducted at relatively low temperatures.⁴ The reduction of the octalone to *cis*-9-methyl-1-decalone was carried out as has been described (3).

⁴ This method of Fieser and Hershberg had been employed by several investigators for ring closure onto aromatic rings. Recently Johnson and co-workers, *J. Am. Chem. Soc.*, **67**, 1360 (1945), employed this mixture at reflux temperature for the preparation of unsaturated five-membered ring ketones. Under these conditions we obtained only 20-35% yields of three of our four six-membered ring ketones in contrast to the 75-96% yield obtained at lower temperatures.

cis-9-Methyl-1-decalone with methyl γ -bromocrotonate and zinc gave the unsaturated Reformatsky ester, which was hydrogenated and subsequently dehydrated and hydrolyzed to γ -9-methyl- Δ^1 -1-*cis*-octalinbutyric acid (VII).⁵ Cyclization by the zinc chloride-acetic anhydride method afforded *cis*-1-keto-4b-methyl- Δ^{4a-10a} -dodecahydrophenanthrene (IX)^{5, 6} in 84% yield. In accord with

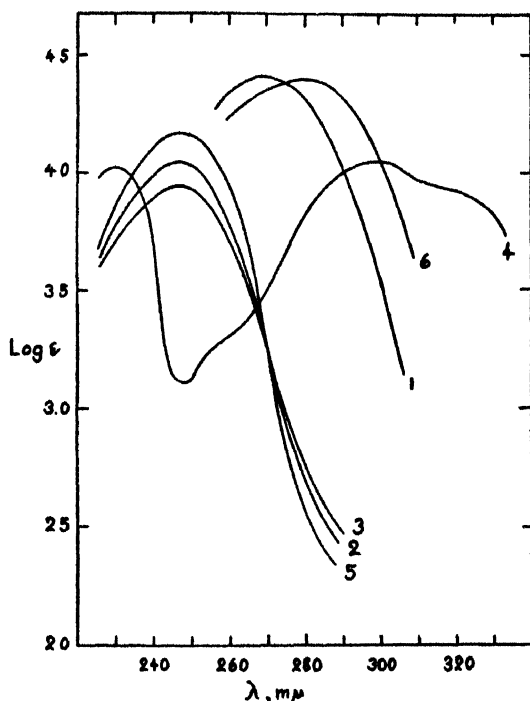


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA

- Curve 1: III, 2-methyl-2-carboxycyclohexylidenecrotonic acid.
 Curve 2: IX, *cis*-1-keto-4b-methyl- Δ^{4a-10a} -dodecahydrophenanthrene.
 Curve 3: X, 1-keto- Δ^{4a-10a} -dodecahydrophenanthrene.
 Curve 4: Xa, 1-keto-1,2,3,4,9,10-hexahydrophenanthrene.
 Curve 5: XIII, *cis*-1-keto-2,4b-dimethyl- Δ^{4a-10a} -dodecahydrophenanthrene.
 Curve 6: XV, *cis*-2,4b-dimethyl- Δ^{4a-10a} -dodecahydro-1-phenanthrylideneacetic acid.

the proposed structure, the ketone showed the characteristic absorption spectrum (maximum at 247 $m\mu$; $\log \epsilon = 4.0$; curve 2) of α,β -unsaturated ketones (4).

The same cyclization method applied to the corresponding deamethyl unsaturated acid VIII yielded the unsaturated cyclic ketone X, identical with that

⁵ The prefix *cis* refers to the configuration between the rings (A and B rings for the polycyclic compounds).

⁶ While this paper was being written, the abstract of a paper by Banerjee, *Science and Culture*, 12, 508 (1947); *Chem. Abstr.*, 41, 6557 (1947), appeared describing the preparation of this ketone by another method. We have also learned from Professor J. W. Cook that he and his co-workers have prepared the ketone through the use of methyl γ -bromocrotonate.

obtained by the stannic chloride method (1). The structure X received confirmation from the ultraviolet absorption spectrum (maximum at $247\text{ m}\mu$; $\log \epsilon = 3.9$; curve 3) (4, 5). A similar cyclization of γ -3,4-dihydro-1-naphthalenebutyric acid (1) gave 1-keto-1,2,3,4,9,10-hexahydrophenanthrene (Xa) in nearly quantitative yield (5). The unsaturated cyclic ketone showed the strong absorption maxima (curve 4) at $232\text{ m}\mu$ ($\log \epsilon = 4.1$) and at $300\text{ m}\mu$ ($\log \epsilon = 4.1$) characteristic of the triply conjugated system: benzene ring—double bond—keto group (4).⁷

The unsaturated ketone IX reacted smoothly with dimethyl oxalate in the presence of sodium methoxide. Pyrolysis of the crystalline glyoxalate (XI) gave the β -keto ester, *cis*-1-keto-2-carbomethoxy-4b-methyl- Δ^{4a-10a} -dodecahydrophenanthrene (XII), which on methylation gave *cis*-1-keto-2-carbomethoxy-2,4b-dimethyl- Δ^{4a-10a} -dodecahydrophenanthrene (XIV). Decarboxylation of the acid derived from (XIV) afforded *cis*-1-keto-2,4b-dimethyl- Δ^{4a-10a} -dodecahydrophenanthrene (XIII), whose absorption spectrum (maximum at $247\text{ m}\mu$; $\log \epsilon = 4.1$; curve 5) showed it to be an α,β -unsaturated ketone (4). The ketone was transformed into the unsaturated acid, *cis*-2,4b-dimethyl- Δ^{4a-10a} -dodecahydro-1-phenanthrylideneacetic acid (XV) through the Reformatsky reaction. The ultraviolet absorption spectrum (maximum at $280\text{ m}\mu$; $\log \epsilon = 4.4$; curve 6) showed it to be an $\alpha,\beta,\gamma,\delta$ -diene acid (2), in agreement with the proposed structure XV. This acid, as well as XIII and XIV should prove useful for preparing the desoxyandrosterone structure.

We are indebted to the Monsanto Chemical Company for a grant which was used to provide support for Andre Dreiding during this investigation.

EXPERIMENTAL

Dimethyl ester of γ -2-methyl-2-carboxy-1-hydroxycyclohexanecrotonic acid (I). 2-Carbomethoxycyclohexanone was prepared according to the method described for the corresponding ethyl ester (6); an equal volume of absolute methanol was used to dissolve the dimethyl oxalate. The second distillation of the keto ester was carried out with a six-inch column; b.p. $95-107^\circ$ (30 mm.); yield, 43%. The keto ester was methylated by the procedure described for the ethyl ester (7); yield, 90%; b.p. $69-72^\circ$ (0.4 mm.); n_D^{25} 1.4570.

A mixture of 20 g. of 2-methyl-2-carbomethoxycyclohexanone, 10 g. of methyl γ -bromocrotonate, and 20 g. of cleaned zinc (20 mesh) in 50 cc. of anhydrous ether and 50 cc. of dry reagent benzene was heated nearly to the boiling point. A few small crystals of iodine were added and allowed to rest on the zinc without agitation. Within a few minutes the iodine color disappeared and a white cloud rose from the zinc at the point where the iodine had attacked it. This indicated the start of the reaction, which proceeded with slight evolution of heat as an additional 46 g. of methyl γ -bromocrotonate was added slowly over a period of about two hours. The mixture was kept refluxing for four hours more. Fresh zinc was added in 5-g. batches at hourly intervals during the first three hours. The complex was dissolved by the addition of 25 cc. of glacial acetic acid. When the solution was clear, it was decanted from the excess zinc into ice-cold water. The zinc salts were removed by extraction with ten 50-cc. portions of 1% ammonium hydroxide. The crude Reformatsky ester, obtained by concentrating the solution, was distilled through a two-inch fractionating column, b.p. $135-145^\circ$ (0.05 mm.); yield, 26.66 g. (84%); n_D^{25} 1.4900.

⁷ Wilds and co-workers, *J. Am. Chem. Soc.*, **69**, 1985 (1947), have recently examined the ultraviolet absorption spectra of a series of compounds with related structures, including this ketone. Our results are in agreement.

Anal. Calc'd for $C_{14}H_{22}O_4$: C, 62.20; H, 8.20.

Found: C, 62.87; H, 8.49.

2-Methyl-2-carboxycyclohexylidenecrotonic acid (III). A solution of the unsaturated Reformatsky ester (I) (1.5 g.) in 5 cc. of ether was added dropwise to a chilled mixture of 1.4 cc. of pure thionyl chloride, 0.8 cc. of pyridine, and 5 cc. of ether. After one hour at 0°, the precipitated pyridine hydrochloride was dissolved by the addition of small pieces of ice. The excess of thionyl chloride in the organic layer was decomposed by extraction with a sodium bicarbonate solution until no more carbon dioxide was evolved. The solvent was removed and the residual oil refluxed for ten hours in a solution of 2.5 g. of potassium hydroxide in 17 cc. of absolute methanol. Some methanol was removed *in vacuo*, and the residue acidified with cold dilute hydrochloric acid. The crude acid precipitated as a cream colored solid; yield, 0.98 g. (82%), m.p. 196–206°. Recrystallization from aqueous methanol yielded colorless short needles, m.p. 205.5–207° (softening at 195°).⁸

Anal. Calc'd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19.

Found: C, 64.53; H, 7.06.

Refluxing the Reformatsky ester (I) in acetic anhydride for one hour did not remove water from the molecule, as evidenced by the fact that the product absorbed only one mole of hydrogen on catalytic reduction. Whether esterification of the hydroxyl group had taken place was not determined.

γ-2-Methyl-2-carboxy-1-hydroxycyclohexanebutyric acid (V). A solution of 24.5 g. of the Reformatsky ester (I) was hydrogenated in methanol in the presence of 0.20 g. Adams' catalyst. Within five minutes, one mole equivalent of hydrogen was consumed. The catalyst was removed by filtration and the solvent removed in a stream of dry air. The residual colorless oil (24.8 g.) was used in part directly for the dehydration described in (a) of the next experiment.

A portion was distilled at 130–135° (0.2 mm.). A mixture of 2.5 g. of this distillate, 25 cc. of 40% potassium hydroxide, and 50 cc. of methanol was refluxed for one and one-half hours. Some of the methanol was removed in a stream of dry air, and the residual solution was acidified with cold dilute hydrochloric acid. An oil precipitated which solidified on standing in the cold for several days; weight, 1.52 g. (68%), m.p. 63–69°. Recrystallization from 20% acetic acid afforded elongated colorless prisms, m.p. 73°; yield, 1.25 g. For analysis, a sample was recrystallized from 50% ether-petroleum ether (b.p. 60–75°); m.p. 77.5°.

Anal. Calc'd for $C_{12}H_{20}O_5$: C, 58.90; H, 8.25.

Found: C, 59.06; H, 8.16.

The hydroxy acid (V), m.p. 73°, with diazomethane, yielded the dimethyl ester, which was evaporatively distilled at 130–132° (0.2 mm.), n_D^{20} 1.4519. Dehydration of the latter could not be accomplished by mild methods. Thus, treatment, for one hour, of the ester with acetic anhydride or dry hydrogen chloride gas in boiling benzene and subsequent saponification resulted only in recovery of the hydroxy acid (V).

When the hydroxy acid (V) was pyrolyzed at 220° for thirty minutes and the product subjected to evaporative distillation *in vacuo*, an oil distilled at 110–130° (0.8 mm.). This was dissolved in the minimum amount of hot 50% aqueous methanol and treated with Norit. After filtration and cooling, fine colorless plates of *γ*-2-methyl- Δ^1 -cyclohexenebutyric acid precipitated, m.p. 39°. On recrystallization from the same solvent, it melted at 45.5–46° [reported (3c), 44°]. Neutral equivalent: 182 (requires 182). It combined rapidly with bromine in carbon tetrachloride.

cis-γ-2-Methyl-2-carboxycyclohexanebutyric acid (IV). (a) *From the saturated hydroxy ester (dimethyl ester of V).* To a cold solution of 10 cc. of dried pyridine in 35 cc. of anhydrous ether was added 18 cc. of thionyl chloride (Eastman Kodak, white label, is sufficiently pure). A colorless precipitate dissolved on swirling and a clear yellow solution resulted. To this was added dropwise, with swirling and cooling, a solution of 20 g. of the hydroxy

⁸ The ultraviolet absorption spectrum of the compound was taken in dilute alcoholic solution with a Beckman spectrophotometer. The oximes absorbed in the same region as the corresponding ketones.

ester (dimethyl ester of V) in 35 cc. of anhydrous ether. After the first few drops, a pyridine salt precipitated. The addition required about fifteen minutes, after which the solution was half filled with a fluffy white precipitate. The mixture was allowed to stand for one hour at 0°. It was poured on cracked ice and, after all the solid had dissolved, the aqueous layer was discarded. The excess thionyl chloride in the organic layer was decomposed by the cautious addition of sodium bicarbonate solution. When no more carbon dioxide was evolved, the solution was extracted with 10% sodium carbonate and water. After drying and filtering, the solvent was removed in a stream of dry air. The residual pale yellow oil was refluxed in a solution of 240 cc. of 18% methanolic potassium hydroxide for twelve hours. About half of the methanol was removed in a stream of dry air and replaced by water. The resulting clear amber solution was heated on a steam-bath for two hours and acidified cold by pouring it into a cold mixture of 150 cc. of 10% hydrochloric acid and 50 cc. of ether. The aqueous layer was drawn off and extracted again with ether. The combined organic layers were washed with water, dried, and concentrated. The crude unsaturated acid was obtained as a viscous oil; yield, 16.2 g.

The above mentioned oil was dissolved in 150 cc. of glacial acetic acid and shaken under 30 lbs. of hydrogen at room temperature in the presence of 0.2 g. of Adams' catalyst for twenty-four hours. Only a small amount of hydrogen was consumed and 0.2 g. of fresh catalyst was added. After further hydrogenation for twenty-four hours, almost the theoretical amount of hydrogen had been taken up. Continued hydrogenation with an additional batch of 0.2 g. of fresh catalyst caused the reduction to reach completion. The catalyst was filtered off and the colorless filtrate was concentrated in a stream of dry air on a steam-bath. The residual colorless oil was dissolved in 100 cc. of methanol, and 100 cc. of water was added. The mixture was heated in the presence of charcoal, filtered, and allowed to cool slowly. On seeding and scratching, *cis-γ-2-methyl-2-carboxycyclohexanebutyric acid* (IV) crystallized in colorless rhombs; yield, 11.92 g. (71%, based on the crude hydroxy ester, and 59%, based on 2-methyl-2-carbomethoxycyclohexanone); m.p. 106–110°. This sample was used for the cyclization experiments described below. A portion, recrystallized from 50% aqueous methanol, melted at 111.5–112° [reported (1) 109–112°].

From the mother liquors, 3.35 g. of an oily acid was obtained. It was not characterized with certainty; it could, however, be cyclized by the methods described below to a camphoraceous ketone.

(b) *From the diene acid (III)*. A solution of 0.26 g. of the diene acid (III) in 5 cc. of glacial acetic acid was shaken under one atmosphere of hydrogen at room temperature in the presence of a trace of Adams' catalyst. Two mole equivalents of hydrogen were absorbed in twenty minutes. No break after the consumption of one mole could be observed. The catalyst and solvent were removed and the *cis*-acid (IV) crystallized from aqueous methanol; yield, 0.42 g. (92%), m.p. 108–110°. After recrystallization from the same solvent, it melted at 111.5–112° [reported (1) 109–112°]. Hydrogenation of the diene acid in the form of its sodium salt in aqueous solution with Adams' catalyst also yielded only the *cis*-acid (IV), m.p. 111.5–112°.

(c) *In form of its dimethyl ester through an Arndt-Eistert reaction*. The dimethyl ester of *cis*-β-2-methyl-2-carboxycyclohexanepropionic acid (7) (1.05 g.) was half-hydrolyzed and the product subjected to an Arndt-Eistert reaction according to the procedure described for the lower homolog (7). In this manner the dimethyl ester of *cis*-γ-2-methyl-2-carboxycyclohexanebutyric acid (IV) was obtained. It was evaporatively distilled, b.p. 105–110° (0.02 mm.); yield, 0.62 g. (56%). When this ester was cyclized according to the Dieckmann method, described below, 0.31 g. (77%) of *cis*-9-methyl-1-decalone was obtained. The melting points, mixed melting points, and crystalline forms of the oxime and of the 2,4-dinitrophenylhydrazones showed that this sample of the ketone was identical with the one obtained by the method involving the methyl γ-bromocrotonate Reformatsky reaction.

cis-9-Methyl-1-decalone. (a) *By a Dieckmann condensation on the dimethyl ester of IV*. The procedure described here represents a modification and improvement of the one re-

ported (1). The dimethyl ester (27.97 g.) was made from 25.6 g. of the diacid (IV) [m.p. 106–110°; this sample was made by the method described in (a) of the previous experiment] with diazomethane and distilled; b.p. 124–125° (0.4 mm.). Dry sodium methoxide, made from 6.15 g. of clean sodium, was covered with a solution of the ester in 45 cc. of dry reagent benzene. The flask, which was kept filled with nitrogen, was fitted with a goose-neck tube and a receiver. Heat was supplied at such a rate that the benzene distilled into the receiver at a very slow rate. After five hours of heating, the residual light-brown cake was treated with a chilled mixture of 150 cc. of water and 40 cc. of glacial acetic acid. The oil which separated was taken up in ether, washed with sodium bicarbonate solution and water, dried, and concentrated. The residual *cis*-9-methyl-2-carbomethoxy-1-decalone was a pale yellow oil, sufficiently pure for the next step. In some runs, it was evaporatively distilled, b.p. 90–100° (0.4 mm.). The distillate was a colorless oil which gave a purple color with alcoholic ferric chloride.

The crude keto ester was heated up slowly in a solution of 230 cc. of glacial acetic acid, 130 cc. of concentrated hydrochloric acid, and 30 cc. of water in an atmosphere of nitrogen. When the temperature of the solution reached 90–95°, the decarboxylation started, proceeded very vigorously for twenty minutes, more slowly for another twenty minutes, and then ceased. The mixture was diluted with an equal amount of water, saturated with salt, and extracted with ether. The ethereal solution was washed with 10% sodium hydroxide solution until all the acidic material was removed and then with water. After it was dried, the solvent was removed and the residue distilled; b.p. 68–70° (0.2 mm.); yield, 16.23 g. (90%), n_D^{20} 1.4890. On acidification of the alkaline extracts, 2.65 g. of *cis*- γ -2-methyl-2-carbomethoxycyclohexanecarboxylic acid (monomethyl ester of IV) was obtained as an oil. It was evaporatively distilled at 110–120° (0.3 mm.). This accounted for the 10% of the diester which did not cyclize, and which was half-hydrolyzed under the conditions of the decarboxylation. It was re-esterified and made to undergo the Dieckmann reaction, hydrolysis, and decarboxylation. In this manner an additional 1.65 g. of *cis*-9-methyl-1-decalone was obtained, increasing the yield to 17.88 g. (99%).

(b) *By the action of acetic anhydride on the diacid (IV) and pyrolysis of the product.*⁹ A solution of 1 g. of the *cis*-dibasic acid (IV) in 10 cc. of acetic anhydride was refluxed for two hours. The acetic acid and anhydride were distilled at atmospheric pressure, the residue was heated at 200° for twenty minutes, and the crude product was distilled at 215–225°. The yellow distillate was heated in 10 cc. of glacial acetic acid, 4 cc. of concentrated hydrochloric acid, and 1 cc. of water for one hour. The solution was cooled, saturated with salt, and extracted with ether. The acidic material was removed by extraction with alkali and water. Colorless ketone was obtained by evaporative distillation at 60–70° (0.08 mm.); yield, 0.31 g. (41%). Its oxime melted at 114–115°.

Methyl γ -2-methyl-1-hydroxycyclohexanecrotonate (II). The Reformatsky reaction between 10 g. of 2-methylcyclohexanone and 20 cc. of methyl γ -bromocrotonate in the presence of 10 g. of granulated zinc was conducted in the manner described for the reaction on the 2-carbomethoxy derivative. The crude oil was fractionally distilled through a two-inch column, b.p. 112–116° (0.02 mm.); yield, 15.03 g. (80%). The colorless distillate decolorized bromine in carbon tetrachloride.

Anal. Calc'd for $C_{12}H_{20}O_3$: C, 67.82; H, 9.47.

Found: C, 67.21; H, 9.24.

Methyl ester of γ -2-methyl-1-hydroxycyclohexanecarboxylic acid (VI). A solution of 13 g. of the above Reformatsky ester (II) in 50 cc. of absolute methanol was shaken in the presence of 0.1 g. of Adams' catalyst under 30 lbs. of hydrogen at room temperature. The theoretical amount of hydrogen was consumed in thirty minutes. The colorless solution was filtered and concentrated *in vacuo* at room temperature. The residual hydroxy ester was distilled through a two-inch column at 85–95° (0.05 mm.); weight, 11.8 g. (90%). The

⁹ Kon, Linstead, and Simon, *J. Chem. Soc.*, 814 (1937) cyclized this acid (prepared in non-crystalline form by another method) by pyrolyzing it with barium oxide.

colorless distillate did not affect a solution of bromine in carbon tetrachloride. A small fraction was cut at 90° (0.05 mm.) for analysis.

Anal. Calc'd for $C_{11}H_{22}O_3$: C, 67.25; H, 10.35.

Found: C, 67.25; H, 9.91.

γ -2-Methyl- Δ^1 -cyclohexenebutyric acid. A mixture of 9.1 g. of the above hydroxy ester and 20 g. of powdered fused anhydrous potassium acid sulfate was heated on a steam-bath under nitrogen for thirty minutes. The unsaturated ester, isolated by ether extraction, was distilled through a small fractionating column, b.p. 72–76° (0.02 mm.); yield, 7.48 g. (91%). It immediately decolorized aqueous potassium permanganate.

A solution of the above distillate in 20 cc. of 50% potassium hydroxide and 50 cc. of methanol was refluxed for one hour in an atmosphere of nitrogen. Some of the methanol was removed *in vacuo* and the solution was acidified with chilled dilute hydrochloric acid. The yellow oil which partially solidified was extracted with ether and, after drying and removal of the solvent, was distilled *in vacuo* with slight decomposition, b.p. 110–115° (0.05 mm.) yield, 4.95 g. (72%). A portion of the viscous distillate was dissolved in hot aqueous methanol. On cooling, colorless plates appeared, which, after several recrystallizations, melted at 45–46° (3c). The acid instantly decolorized bromine in carbon tetrachloride and aqueous potassium permanganate.

9-Methyl-1-octalone. A solution of 3.74 g. of the above unre-crystallized acid in 37 cc. of acetic anhydride and 7.5 cc. of a 5% solution of fused anhydrous zinc chloride in glacial acetic acid was allowed to stand at room temperature for forty-eight hours and then heated on a water-bath at 70–80° for thirty minutes. The wine red solution was diluted with ether and extracted with ice-cold 5% sodium hydroxide solution until all the anhydride was decomposed and the acid was removed. The ketone, obtained by removal of the solvent, was evaporatively distilled at 70–80° (0.2 mm.); yield, 2.53 g. (75%). The oxime, m.p. 95–95.5° [reported (3a) 99–100° for this oxime or its isomer with the double bond in the alternative position], was prepared in 72% yield, and the semicarbazone, m.p. 227.5–229° [reported, 226–227° (3a), 222–223° (3b), and 228–229° (3c)], in 75% yield. The pure ketone was regenerated by acid hydrolysis of the semicarbazone in 88% yield; b.p. 70–75° (0.2 mm.).⁸ The ultraviolet absorption spectrum showed no maximum in the region of 220–340 $m\mu$, and the intensity of absorption in that region was low ($\log \epsilon < 3$). This showed that the unsaturation was not conjugated with the keto group.

Methyl γ -9-methyl-1-hydroxy-1-cis-decalincrotonate. A mixture of 5 g. of *cis*-9-methyl-1-decalone, 2.5 g. of methyl γ -bromocrotonate, and 5.5 g. of clean zinc turnings in 15 cc. of anhydrous ether and 15 cc. of dry reagent benzene was heated. Before the solution started to boil, a few small crystals of iodine were added and were allowed to rest on the zinc without agitation. Within a short while, the reaction started, as evidenced by the disappearance of the iodine color and the rising of a white cloud from the zinc. The reaction became slightly exothermic and remained so while an additional 7.5 g. of methyl γ -bromocrotonate was added slowly from a dropping-funnel. When the reaction was well under way, stirring was started at moderate speed. The addition of bromo ester took about three hours; after this, the solution was kept refluxing for another two hours. During the reaction, batches of 2.5 g. of fresh zinc were added at hourly intervals. The yellow complex was decomposed by the addition of excess glacial acetic acid. Cold water and ether were added and the organic layer was washed with as many portions of 1% ammonium hydroxide as needed to remove the zinc salts, and then with water. From the ethereal solution was obtained 8.8 g. of the crude Reformatsky ester. It contained some unreacted ketone, as will be shown below. In some experiments it was distilled with some decomposition, b.p. 160–170° (0.1 mm.). The distillate was a slightly yellow viscous oil. For the continuation of the synthesis a purification was not necessary; the unreacted ketone could be recovered at a later stage.

γ -9-Methyl- Δ^1 -1-cis-octalinbutyric acid (VII). The crude Reformatsky ester (8.8 g.) was catalytically reduced in 35 cc. of absolute methanol at room temperature under one atmosphere of hydrogen in the presence of 0.2 g. of Adams' catalyst. The solution was

filtered, the solvent was removed, and the oily residue was heated with 20 g. of powdered fused anhydrous potassium acid sulfate in an atmosphere of nitrogen for one hour on a steam-bath. The product, which was isolated by use of ether, and a solution of 13 cc. of 40% potassium hydroxide and 25 cc. of methanol were refluxed for one and one-half hours on a steam-bath under nitrogen. The solution was diluted with water, saturated with salt, and extracted with ether. From the ethereal solution 1.95 g. (39%) of unreacted *cis*-9-methyl-1-decalone was recovered; after evaporative distillation at 0.4 mm. it gave the same yield of Reformatsky product as did the starting ketone. The alkaline solution was acidified with cold dilute hydrochloric acid. The unsaturated acid (VII) was extracted with ether, and the ethereal solution was washed with water, dried, and concentrated *in vacuo* at room temperature; yield of pale yellow oil, 3.14 g. This crude acid was usually used directly for the cyclization. In some experiments it was evaporatively distilled at 143–150° (0.02 mm.). The distillate was a colorless viscous oil which resisted attempts at crystallization. It decolorized both bromine in carbon tetrachloride and aqueous potassium permanganate slowly. The *p*-bromophenacyl ester crystallized in fine colorless needles from aqueous ethanol, m.p. 67–69°.

Anal. Calc'd for $C_{22}H_{20}BrO_2$: C, 63.74; H, 6.74; Br, 18.44.

Found: C, 63.17; H, 6.85; Br, 18.97.

cis-1-Keto-4 β -methyl- Δ^{4a-10a} -dodecahydrophenanthrene (IX). A solution of 3.14 g. of the crude unsaturated acid (VII) in 43 cc. of reagent acetic anhydride and 8.6 cc. of a 5% solution of anhydrous fused zinc chloride in glacial acetic acid was allowed to stand at room temperature under nitrogen for twenty hours. The wine red solution was heated at 70° for one hour. Ether was added and the acetic anhydride was decomposed by extraction with chilled 5% sodium hydroxide. From the alkaline extracts a small amount of uncyclized acid could be recovered. The crude ketone (IX), obtained from the ethereal solution, was evaporatively distilled at 105–115° (0.2 mm.); yield, 2.44 g. (84%).⁸ The colorless distillate decolorized aqueous potassium permanganate solution slowly. The derivatives were obtained by standard methods. The *oxime* crystallized from aqueous methanol in clusters of colorless needles, m.p. 134–135.5°.

Anal. Calc'd for $C_{16}H_{22}NO$: C, 77.20; H, 9.95; N, 6.00.

Found: C, 77.01; H, 9.72; N, 6.33.

The *semicarbazone* crystallized from methanol in clusters of colorless prisms, m.p. 229–231°.

Anal. Calc'd for $C_{16}H_{22}N_2O$: C, 69.78; H, 9.15.

Found: C, 69.82; H, 9.63.

The *2,4-dinitrophenylhydrazone* crystallized from ethyl acetate in scarlet threads, m.p. 228.5–229.5°.

Anal. Calc'd for $C_{21}H_{20}N_4O_4$: C, 63.30; H, 6.58; N, 14.06.

Found: C, 63.10; H, 6.46; N, 13.91.

1-Keto- Δ^{4a-10a} -dodecahydrophenanthrene (X). The crude unsaturated acid (VIII) (1) (2.5 g.) was cyclized in the manner described for IX. The crude ketone was evaporatively distilled at 80–100° (0.05 mm.); yield, 1.42 g. (62%). The scarlet 2,4-dinitrophenylhydrazone, after recrystallization from ethyl acetate, melted at 229–230° d. [reported (1) 215–216° d.]. The *oxime*, m.p. 142–145°, was prepared in 88% yield. A small portion, recrystallized from dilute methanol and then from petroleum ether (b.p. 65–70°), formed glistening elongated prisms, m.p. 171.5–173.5°.

Anal. Calc'd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39.

Found: C, 76.81; H, 9.22; N, 6.40.

The pure ketone was obtained from a boiling (three hours) solution of 0.31 g. of the *oxime* (m.p. 144–146°) in 3.8 cc. of 15% hydrochloric acid and 10 cc. of ethanol. The ketone was extracted and evaporatively distilled at 100–109° (0.05 mm.);⁸ yield, 0.28 g. (90%).

Cyclization of γ -3,4-dihydro-1-naphthalenebutyric acid by acetic anhydride and zinc chloride. The acid (1) (0.66 g.) was cyclized in the manner described for IX. The crude 1-keto-1,2,3,4,9,10-hexahydrophenanthrene (Xa) was evaporatively distilled at 90–100°

(0.02 mm.); yield, 0.58 g. (96%). The 2,4-dinitrophenylhydrazone, m.p. 238–242°, was obtained in quantitative yield. After two recrystallizations from ethyl acetate, it formed fine magenta needles, m.p. 259–260°.

Anal. Calc'd for $C_{20}H_{12}N_4O_4$: C, 63.48; H, 4.80; N, 14.81.

Found: C, 63.27; H, 4.88; N, 14.77.

The oxime crystallized from aqueous methanol in stout colorless needles, m.p. 142–143° [reported, 140.5–141.5° (1), 141.5–142° (8)]. The semicarbazone, after recrystallization from aqueous methanol, melted at 254–258° d. [reported (8) 257–258°]. The crystalline ketone was obtained by hydrolyzing 0.31 g. of the oxime (m.p. 142–143°) in 3.8 cc. of 15% hydrochloric acid and 10 cc. of ethanol on a steam-bath for three hours under nitrogen. The ketone was extracted with ether, evaporatively distilled (at 85–95° and 0.02 mm.; yield, 0.25 g.) and recrystallized twice from ether-petroleum ether; m.p. 48–49° [reported 48–49° (1), 49–50° (8)]; yield, 0.20 g. (65%).

cis-Methyl 1-keto-4b-methyl- Δ^{4a-10a} -dodecahydro-2-phenanthreneglyoxalate (XI). Dry sodium methoxide (from 0.25 g. of sodium) and 1 g. dimethyl oxalate were suspended in 56 cc. of dry benzene. A solution of 0.82 g. of the unsaturated ketone (IX) in 4 cc. benzene was added dropwise while the mixture was kept under nitrogen at 0°. After standing at room temperature for two hours, the solution was treated with cold water, a little 5% sodium hydroxide, and ether. The aqueous layer was drawn off and the organic layer extracted with some more alkali. From the ethereal solution, about 3% of unreacted ketone could be recovered. The combined alkaline layers were washed with ether and acidified with cold 10% hydrochloric acid. The precipitate was taken up in ether and, after concentrating, a golden viscous oil was obtained; yield, 1.10 g. (95%). The glyoxalate solidified upon standing in the cold; it was placed on a Büchner funnel, pressed, and washed with a few drops of cold methanol; m.p. 75–78°; weight, 1 g. From the mother liquor, another 0.08 g. of solid glyoxalate was obtained by evaporating and treating with a few drops of methanol; total yield, 1.08 g. (94%). A sample crystallized from absolute methanol in elongated cream colored prisms, m.p. 76.5–77.5°.

Anal. Calc'd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95.

Found: C, 71.24; H, 8.04.

The glyoxalate gives a dark red-brown color with alcoholic ferric chloride. It is insoluble in sodium bicarbonate but soluble in 5% sodium hydroxide solution. When an alkaline solution of the glyoxalate was allowed to stand at room temperature for several days, the parent ketone (IX) precipitated.

cis-2-Carbomethoxy-1-keto-2,4b-dimethyl- Δ^{4a-10a} -dodecahydrophenanthrene (XIV). A mixture of 0.61 g. of the glyoxalate and 2 g. of powdered glass (9) was slowly heated in a test-tube under an atmosphere of nitrogen. At a bath temperature of 158° the evolution of carbon monoxide started and continued until the temperature had reached 170° after ten minutes. During the next three minutes the bath temperature rose to 175° but no additional gas was evolved. Exactly the theoretical amount (48 cc. at 22°) of gas was collected in a gas burette. The gas burned with a dull blue flame. The residue was taken up in ether and the ethereal solution washed with 5% sodium hydroxide solution to remove any unreacted glyoxalate. After removal of the ether, the keto ester (XIV) was obtained as a dark viscous oil; yield, 0.53 g. It gave a green color with alcoholic ferric chloride.

This oil, dissolved in 4 cc. of dry benzene, was added to a cold solution of 0.47 g. of sodium methoxide in 6.0 cc. anhydrous methanol. Methyl iodide (1.8 cc.) was added and the mixture was allowed to stand at 0° for one hour. Another 0.8 cc. of methyl iodide was added and the solution again allowed to stand at 0° for one-half hour and then at room temperature for fifteen hours. The solution, which was now neutral to moist litmus paper, was concentrated and water, ether, and salt were added. The ethereal solution was washed with 5% sodium hydroxide and water, dried, and filtered through a small column of activated alumina. The filtrate was concentrated and the residue evaporatively distilled at 125–135° (0.05 mm.); yield, 0.55 g. (87%). The colorless viscous keto ester (XIV) slowly decolorized aqueous potassium permanganate.

cis-1-Keto-2,4*b*-dimethyl- Δ^{4a-10a} -dodecahydrophenanthrene (XIII). For the decarboxylation, 0.235 g. of the methylated keto ester (XI) was dissolved in a solution of 5 cc. of 20% potassium hydroxide and 10 cc. of methanol. The mixture was refluxed under nitrogen for fifteen hours. After cooling, it was diluted with water, saturated with salt and extracted with ether. The crude ketone was evaporatively distilled at 90–100° (0.02 mm.); yield, 0.177 g. (94%).⁸ The colorless oil slowly decolorized aqueous potassium permanganate. The *ozime*, which formed readily, crystallized from methanol with a little water in colorless rhombs; m.p. 196–197°.

Anal. Calc'd for $C_{18}H_{28}NO$: C, 77.68; H, 10.19; N, 5.66.

Found: C, 78.02; H, 9.99; N, 5.86.

The 2,4-dinitrophenylhydrazone, which formed more sluggishly than with the two lower homologs (IX and X), crystallized from methanol-ethyl acetate in fine scarlet needles, m.p. 159–161°.

Anal. Calc'd for $C_{22}H_{28}N_4O_4$: C, 64.06; H, 6.84; N, 13.58.

Found: C, 64.30; H, 6.72; N, 13.30.

cis-2,4*b*-Dimethyl- Δ^{4a-10a} -dodecahydro-1-phenanthrylideneacetic acid (XV). A mixture of 0.12 g. of the unsaturated ketone (XIII), 0.3 g. of cleaned granulated (20 mesh) zinc, and 0.1 cc. of methyl bromoacetate in 1.5 cc. of ether and 2.0 cc. of reagent benzene was heated to reflux with a crystal of iodine. The Reformatsky reaction started after ten minutes. Reflux was continued for twenty-four hours during which time four equal portions of fresh zinc and methyl bromoacetate were added. The yellow complex was decomposed with acetic acid and water. The Reformatsky ester was purified by extraction with 1% ammonium hydroxide solution. The crude product was treated with 0.18 cc. of thionyl chloride in benzene in the presence of 0.12 cc. of pyridine at 0°. After an hour, the excess thionyl chloride was decomposed by the addition of ice and extraction with sodium bicarbonate solution. The solvents were removed *in vacuo*, and the residue was refluxed in 4 cc. of 10% methanolic potassium hydroxide for five hours. Extraction with ether afforded 0.03 g. of unreacted ketone (XIII). The alkaline solution was acidified cold and extracted with ether. The ethereal solution was dried and concentrated. Upon addition of a few drops of absolute methanol, the crude residue crystallized; yield, 0.08 g. (57%); m.p. 188–194°. It crystallized in almost quantitative yield from glacial acetic acid in clusters of colorless leaflets,⁸ m.p. 212–213° (soon after melting, the clear liquid evolved bubbles).

Anal. Calc'd $C_{18}H_{26}O_2$: C, 78.79; H, 9.55.

Found: C, 78.97; H, 9.54.

The acid immediately decolorized aqueous potassium permanganate.

All analyses were performed by Micro-Tech Laboratory, Skokie, Ill

SUMMARY

The Reformatsky reaction with methyl γ -bromocrotonate was applied to *cis*-9-methyl-1-decalone and 2-methylcyclohexanone. From the products, δ , ϵ -unsaturated acids were obtained. These and two others were cyclized by zinc chloride-acetic anhydride to unsaturated ketones in good yields. Evidence for the structure of some of these ketones was obtained by demonstrating by their ultraviolet absorption spectra, that the double bond was located α , β to the keto group. In the same manner, two doubly unsaturated acids were shown to be α , β , γ , δ -diene acids.

Several important intermediates for the synthesis of the desoxyandrosterone structure, containing the first three rings and functional groups for the attachment of the fourth ring, were synthesized.

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A NEW APPLICATION OF REDUCTIVE ACETYLATION

MORITZ KOHN¹ AND OSKAR KRASSO*Received March 26, 1947*

In the reductive acetylation of 2,4,6-tribromoresorcinol, as recently reported (1), 4,6-dibromoresorcinol diacetate was obtained. It therefore seemed desirable also to subject nitro compounds to reductive acetylation, for if the procedure is applicable, acetylated amines would be produced directly.

Our experiments have shown that halogenated *o*-nitrophenols react vigorously with zinc dust in acetic anhydride and acetic acid. The mixture is at first dark, but later lightens. Difficulty was encountered in that the products of apparently identical experiment showed different melting points on recrystallization. This was found to be due to incomplete acetylation, for if the dried crude products were boiled for a time with acetic anhydride, material of constant melting point was obtained. Analyses of these products showed them to be the corresponding triacetates.

2,4-Dibromo-6-nitrophenol (I) and 2,4-dichloro-6-nitrophenol (III) were prepared from phenol as previously described (2). The reductive acetylation of I gave the triacetate of 2,4-dibromo-6-aminophenol (II), that of III gave 2,4-dichloro-6-aminophenol triacetate (IV).

4-Chlorophenol was brominated with one mole of bromine to 2-bromo-4-chlorophenol, which was converted to 2-bromo-4-chloro-6-nitrophenol (V). Reductive acetylation of V yielded 2-bromo-4-chloro-6-aminophenol triacetate (VI). Application of the procedure to 2-chloro-4-bromo-6-nitrophenol (VII) gave similarly 2-chloro-4-bromo-6-aminophenol triacetate (VIII).

p-Cresol gives on bromination dibromo-*p*-cresol, which with nitrous acid exchanges a bromine atom for a nitro group to yield 5-bromo-3-nitro-4-hydroxy-1-methylbenzene (3), IX. Reductive acetylation of IX resulted in the triacetate of 5-bromo-3-amino-4-hydroxy-1-methylbenzene (X).

Also, nitro compounds which do not contain a phenolic hydroxyl can be reductively acetylated. The easily accessible 4-bromo-2-nitroanisole (4) (XI) can thus be readily converted to 4-bromo-2-acetamidoanisole (XII).

EXPERIMENTAL

Reductive acetylation of 2,4-dibromo-6-nitrophenol (I) to 2,4-dibromo-6-aminophenol triacetate (II). Ten grams of I is mixed with 70 ml. of acetic anhydride and 15 ml. of gl. acetic acid, 10 g. of zinc dust added cautiously (goggles!), and reflux condenser attached. The reaction is vigorous and the mixture darkens. It is cooled, and zinc dust added from time to time with shaking and breaking of lumps until the liquid is nearly colorless, finally refluxed for a few minutes, and filtered. The zinc dust residue is extracted with acetic acid, the combined filtrates diluted with water, and after a time the white solid is washed with water and dried well in a vacuum. The powdered dry product is refluxed for an hour with 4-5 times its weight of acetic anhydride, poured cold into water, and after a time filtered,

¹ Present address: 536 West 113 Street, New York 25, N. Y.

washed, and crystallized from alcohol; granular rhombohedron-like crystals of m.p. 150°.

Anal. Calc'd for $C_{12}H_{11}Br_2NO_4$: C, 36.64; H, 2.80; N, 3.56; Br, 40.71.

Found: C, 37.19; H, 2.92; N, 3.33; Br, 40.68.

Reductive acetylation of 2,4-dichloro-6-nitrophenol (III) to 2,4-dichloro-6-aminophenol triacetate (IV). The reductive acetylation of III was carried out in the same manner as the preceding experiment. The product from the acetic anhydride treatment gave from alcohol colorless prisms of m.p. 112°.

Anal. Calc'd for $C_{12}H_{11}Cl_2NO_4$: Cl, 23.35; N, 4.61.

Found: Cl, 23.31; N, 4.48.

2-Bromo-4-chloro-6-nitrophenol (V) to 2-bromo-4-chloro-6-aminophenol triacetate (VI). The product crystallizes from alcohol in granular crystals of m.p. 144°.

Anal. Calc'd for $C_{12}H_{11}BrClNO_4$: C, 41.38; H, 3.16; N, 4.02.

Found: C, 41.43; H, 3.05; N, 3.93.

4-Bromo-2-chloro-6-nitrophenol (VII) to 2-chloro-4-bromo-6-aminophenol triacetate (VIII). The compound VIII, obtained by the above procedure, crystallizes from alcohol in granular crystals of m.p. 116°.

Anal. Calc'd for $C_{12}H_{11}BrClNO_4$: C, 41.38; H, 3.16; N, 4.02.

Found: C, 40.99; H, 3.29; N, 4.03.

5-Bromo-3-nitro-4-hydroxy-1-methylbenzene (IX) to 5-bromo-3-amino-4-hydroxy-1-methylbenzene triacetate (X). IX, prepared by the method of Zincke and Emmerich (3), gives on reduction as described, the compound X, which separates from alcohol in granular crystals of m.p. 110°.

Anal. Calc'd for $C_{11}H_{14}BrNO_4$: N, 4.27. Found: N, 4.46.

4-Bromo-2-nitroanisole (XI) (4) to 4-bromo-2-acetamidoanisole (1-methoxy-2-acetamido-4-bromobenzene) (XII). The preparation of XII is carried out as in the above examples, except that the crude, damp product from water is dissolved in a little alcohol, and the dark solution allowed largely to evaporate; the mother liquors are removed, and the product purified from water containing a little acetic acid. The dried product is crystallized from benzene-ligroin; leaflets, m.p. 122°.

Anal. Calc'd for $C_9H_{10}BrNO_2$: C, 44.26; H, 4.10; N, 5.74; Br, 32.79; OCH_3 , 12.70.

Found: C, 44.32; H, 4.13; N, 5.75; Br, 33.20; OCH_3 , 13.01.

SUMMARY

1. A new application of reductive acetylation is described, in which nitro compounds are converted directly to the acetates of the amino compounds. From 2,4-dibromo-6-nitrophenol, 2,4-dichloro-6-nitrophenol, 2-chloro-4-bromo-6-nitrophenol, 4-chloro-2-bromo-6-nitrophenol, and 5-bromo-3-nitro-4-hydroxy-1-methylbenzene, the triacetates of the corresponding aminophenols were obtained.

2. Nitro compounds containing no phenolic group can also be reductively acetylated; 4-bromo-2-nitroanisole gives thus 4-bromo-2-acetamidoanisole.

VIENNA, AUSTRIA

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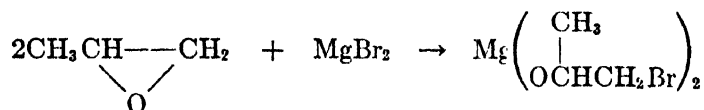
THE REACTION OF PROPYLENE OXIDE WITH ORGANOMAGNESIUM BROMIDES

RALPH C. HUSTON AND CHARLES O. BOSTWICK

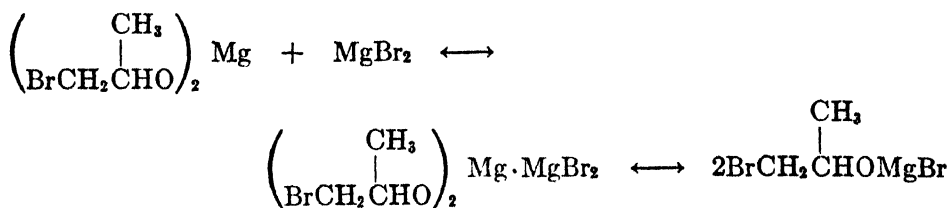
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The addition of one mole of ethylene oxide to one mole of ethylmagnesium bromide resulted in the immediate precipitation of a compound which gave the correct analysis for dibromodiethoxy magnesium and which was hydrolyzed to ethylene bromohydrin (1). The same precipitate was formed immediately when ethylene oxide was added to a solution of magnesium bromide in ether.

The addition of one mole of propylene oxide to one mole of ethylmagnesium bromide caused no precipitation. When propylene oxide was added to a solution of one mole of magnesium bromide, in ether, there was no precipitation during the addition of the first mole. During the addition of the second mole, a precipitate was formed which had a bromine and magnesium content corresponding to dibromodiisopropoxymagnesium,



and which gave upon hydrolysis an 80% yield of propylene bromohydrin. The absence of precipitation during the addition of the first mole and the solubility of dibromodiisopropoxymagnesium in excess of magnesium bromide etherate are attributed to the solubility of bromoisopropoxymagnesium bromide and/or the formation of an addition compound of dibromodiisopropoxymagnesium and magnesium bromide.



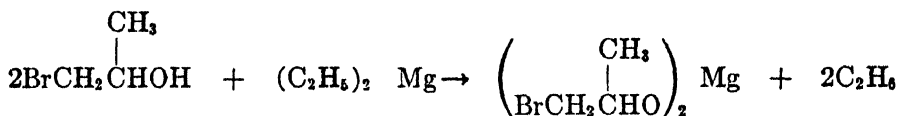
When the reaction is between mole equivalents of propylene oxide and ethylmagnesium bromide, intermediates may be formed by the addition of the propylene oxide to one or both of the bromomagnesium bonds of magnesium bromide, to either the bromomagnesium bond or the ethylmagnesium bond of ethylmagnesium bromide or to both of these or to one or both of the ethylmagnesium bonds of diethylmagnesium.

When mole equivalents of ethylene oxide and ethylmagnesium chloride reacted, the addition was predominantly with the ethylmagnesium bonds, and the yield of butyl alcohol was more than twice as great as that of ethylene chlorohydrin (2), while with the higher alkylmagnesium chlorides, yields of alcohol

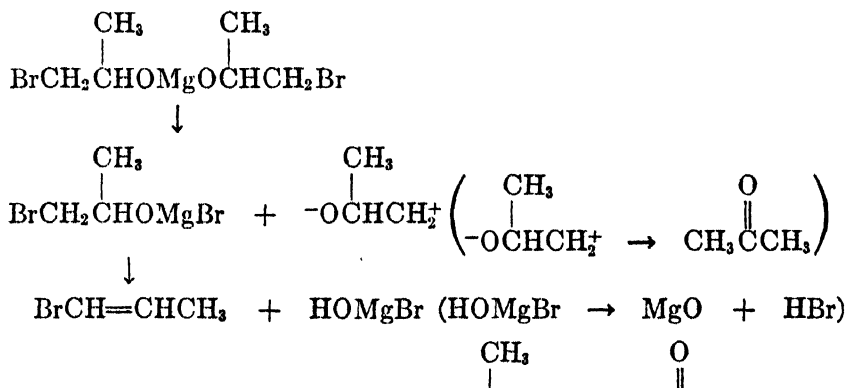
and chlorohydrin were more nearly equal. In some cases, the yield of chlorohydrin exceeded that of the alcohol. It appears that the rate of addition of this epoxide to the alkylmagnesium bond decreases with the increase in size of the alkyl group and with branching.

When one mole of propylene oxide reacted with one mole of ethylmagnesium bromide in the cold and was allowed to stand at room temperature for two days (without refluxing), the addition was predominantly with the magnesium bromide bonds. The yield of propylene bromohydrin was approximately five times that of 2-pentanol (3, 4, 5). In general, reactions of this epoxide with the higher alkylmagnesium bromides give yields of bromohydrin of 60–70% while the yields of secondary alcohols were not greater than seven per cent. With arylmagnesium bromides, on the other hand, yields of alcohols exceeded those of the bromohydrin (Table I).

When the dried precipitate $(\text{BrCH}_2\text{CHO})_2\text{Mg}$, prepared either by treating magnesium bromide solution with propylene oxide or by adding two moles of propylene bromohydrin to one mole of diethylmagnesium, was heated in an atmosphere of nitrogen, it first melted and then decomposed.



Acetone, bromopropylene, and hydrobromic acid distilled over while the residue in the flask became dark colored and viscous. Heating the dibromodiisopropoxymagnesium in air at 500° gave pure magnesium oxide. The following scheme is representative of the type of breakdown involved.



It is proposed that the transformation of -OCHCH_2^+ to $\text{CH}_3\overset{\text{O}}{\underset{||}{\text{CCH}_3}}$ requires the intermediate formation of a protonized double bond.

Attempts to increase the yield of 2-pentanol by heating the reaction mixture of equimolecular equivalents of ethylmagnesium bromide and propylene oxide were not successful (1). When the ether was distilled off and replaced with benzene, refluxing for six hours gave a 24% yield of a mixture of pentanols. This

was separated by fractionation into approximately equal parts of 2-pentanol and 2-methyl-2-butanol which were identified by their boiling points, densities, refractive indices, and 3,5-dinitrobenzoates. There was also isolated a small fraction (4 ml.) of acetone which was identified as its 2,4-dinitrophenylhydrazone. The heating also reduced the yield of bromohydrin from 60% to approximately 10%. These results indicate that, at the boiling temperature of benzene, there is decomposition of dibromodiisopropoxymagnesium and bromoisopropoxymagnesium



bromide with the formation of the fragment -OCHCH_2^+ which rearranges to acetone, which in turn reacts with ethylmagnesium bromide or diethylmagnesium. Cottle and co-workers (6) have also noted the formation of aldehydes and ketones by the decomposition and rearrangement of intermediates formed by the addition of epoxides to Grignard reagents.

When two moles of propylene oxide reacted with one mole of ethylmagnesium bromide, the yield of 2-pentanol was 54% as compared with 13% when the reactants were in a 1.1 ratio, while the yield of bromohydrin was increased from 62% to 76% (Table I). After all of the propylene oxide had been added, a precipitate formed slowly and, within two days, the entire reaction mixture set to a hard mass. In one experiment, the precipitate was removed after twenty hours and dried. Upon hydrolysis, this particular mixture of intermediates yielded bromohydrin and 2-pentanol in a 2:1 ratio.

In all reactions of the series in which two moles of propylene oxide were added to one mole of alkylmagnesium bromide, the mixture was allowed to stand at room temperature until a negative test was obtained with Michler's ketone. In all cases, a very stiff gel or solid was formed.

The yields of secondary alcohols from primary alkylmagnesium bromides, excepting isobutylmagnesium bromide, were more than 50% and from secondary alkylmagnesium bromides more than 30%. Tertiary butylmagnesium bromide required a period of forty-five days to give a negative test with Michler's ketone and gave a yield of 15%. This time is of the same order as that required for the reaction between di-*t*-butylmagnesium and ethylene oxide (1).

In all cases where two moles of propylene oxide were allowed to react with one of alkylmagnesium bromide, there was an evolution of gas which lasted for several days. These gases were passed through bromine and the following alkenes were identified as their dibromides: ethene, propene, 1-butene, 2-butene, and 2-methylpropene. The evolution of gas was most pronounced in the reaction with isobutylmagnesium bromide, which gave the smallest yield of bromohydrin.

In all reactions, small amounts of acetone were isolated from the distillates



which came over at 50–60°. This indicates that some -OCHCH_2^+ is formed and rearranged at or below room temperatures.

There was left a viscous residue after 2-pentanol had been distilled off. A small amount of mesityl oxide was removed by distillation and identified as its 2,4-dinitrophenylhydrazone. It is probable that the residue consisted, for the most part, of polymers and condensation products of both propylene oxide and acetone.

Mesityl oxide was also found as a by-product in the preparation of 2-hexanol, 4-methyl-2-pentanol and 2-heptanol.



The formation of $^-\text{OCHCH}_2^+$ and its rearrangement or polymerization appears to be favored when both propylene oxide and magnesium bromide are present. When propylene oxide was allowed to stand with, or was refluxed with, diethyl-

TABLE I
YIELDS OF ALCOHOLS FORMED BY THE REACTION OF PROPYLENE OXIDE WITH
ORGANOMAGNESIUM BROMIDES

GRIGNARD REAGENT PREPARED FROM	RMgBr + CH_3CHCH_2			RMgBr + 2 CH_3CHCH_2		
	Time (days)	% Yield Bromo- hydrin	% Yield Alcohol	Time (days)	% Yield Bromo- hydrin	% Yield Alcohol
Ethyl bromide...	2	62	13	2	76	54
Propyl bromide...	2	69	4	6	74	51
sec.-Propyl bromide...	2	50	7	7	76	38
n-Butyl bromide...	2	67	5	8	70	56
sec.-Butyl bromide.....	2	62	4	21	62	31
iso-Butyl bromide.....	2	64	4	25	28	15
tert.-Butyl bromide	2	62	4	45	52	15
Phenyl bromide.....	1	39	47	1	74	67
Mesityl bromide.....	1	35	58			

magnesium, 2-pentanol was the only alcohol isolated and there was no evidence of the formation of acetone or of polymerization.

EXPERIMENTAL

Apparatus. For the preparation of Grignard reagents and magnesium bromide etherate and the reaction of these with propylene oxide, a 2-liter, three-necked, round-bottom flask, fitted with a condenser, mercury-seal stirrer, and a Hershberg dropping-funnel or separatory funnel, was used. A nitrogen gas inlet was provided for all reactions. All Grignard reagents and magnesium bromide etherates were protected from atmospheric moisture and CO_2 by calcium chloride and soda-lime tubes. For all distillations a heated glass helix-packed column 12½ in. long was used. The head was of the total reflux, partial take-off, type. The pot was heated with a Glas-col mantle.

Preparation of Grignard reagents. One mole of redistilled organic bromide was mixed with 150 ml. of anhydrous ether (previously dried over sodium for a week). Twenty-six grams of magnesium and 100 ml. of ether were placed in the reaction flask. Ten to fifteen milliliters of the bromide-ether solution was added and the magnesium stirred until reaction started. The aromatic bromides sometimes required refluxing to start the reaction. Two

hundred twenty-five milliliters of ether was then added and the remainder of the bromide-ether solution was added dropwise. The Grignard reagent was stirred over an hour after all of the bromide was in and then allowed to stand under a nitrogen atmosphere overnight.

The aryl and normal alkyl Grignard reagents were prepared by adding the bromide mixture to the uncooled magnesium and ether as fast as the condenser and ice placed on top of the flask would allow. The yield of Grignard reagent was over 90%.

Secondary and iso-alkyl Grignard reagents were prepared by adding the bromide-ether mixture more slowly and not allowing the reaction mixture to get above 35°. The yield of Grignard reagent with isopropyl, *sec.*-butyl, and isobutyl bromide was between 85 and 90%.

tert.-Butylmagnesium bromide was prepared in 50 to 55% yields from the same proportion and quality of reagents. The reaction mixture was cooled in a mixture of salt and ice and the bromide-ether solution added very slowly.

Analysis of the Grignard reagent. The Grignard reagent was forced through a glass wool plug from the unreacted magnesium by nitrogen pressure. Its volume was measured in a 500-ml. graduated cylinder. Five milliliters was pipetted out and analyzed for the organo-magnesium content by Gilman's procedure (7). One milliliter was pipetted out and analyzed by the Volhard method for bromide ion.

Reaction with propylene oxide. The Grignard reagent was poured, under a stream of nitrogen, into the reaction flask filled with nitrogen. This was cooled in salt and ice and a mixture of propylene oxide and an equal volume of ether added slowly. The salt and ice bath was allowed to warm up to room temperature and removed the next day.

When the ratio of reactants was 1:1, the reaction was allowed to stand for two days. With the 1:2 ratio reactions, the reaction mixture was allowed to stand until the test with Michler's ketone was faint or negative.

The reaction mixture was cooled with ice and then 150–200 ml. of saturated ammonium bromide solution was added dropwise. This minimized loss of bromohydrin due to reaction with basic magnesium compounds. The ether solution was decanted from the precipitated magnesium salts and dried over Na_2SO_4 . Water was added to the magnesium salts until they were pasty. This paste was extracted with benzene.

The dried hydrolysis products were refluxed with a mixture of 40 g. of NaOH and 150 ml. of water for one hour with vigorous stirring. The mixture was cooled and the layers separated. The water layer was extracted with benzene, and the benzene and ether extracts dried over Na_2SO_4 . The NaOH layer was heated to boiling to expel excess benzene, cooled, and diluted to one liter. A five-ml. aliquot portion was titrated for bromide ion by Volhard method.

The ether-benzene solution of products was distilled at atmospheric pressure until all of the ether and nearly all of the benzene was removed. For most of the alcohols, reduced pressure was used to prevent decomposition.

In all of the distillations, propylene oxide and acetone were obtained. The acetone was checked by a mixed melting point of its 2,4-dinitrophenylhydrazone. Mesityl oxide (identified by the melting point of its 2,4-dinitrophenylhydrazone) and other unsaturated ketones caused difficulty in the separation of some of the alcohols in the pure state. With several Grignard reactions, a wax-like product was precipitated out of the residue by adding petroleum ether. It has a softening point at 62–63°.

A small fraction (2 ml. or less) was isolated from each reaction mixture, which had a boiling range and refractive index approximately that of the tertiary alcohol that would be formed from acetone and the particular alkylmagnesium bromide. All of these fractions gave positive tests when treated with ceric ammonium nitrate. They were too small and impure to give esters or α -naphthylurethans of definite melting points.

In all reactions of two moles of propylene oxide with one mole of alkylmagnesium bromide, the unsaturated compound corresponding to the alkyl group of the reacting Grignard reagent was isolated from the evolved gases. The gases were passed through bromine and the dibromides were identified by boiling points and refractive indices. No attempt was

made to determine quantitatively the yields of these alkenes. The amounts of dibromide collected in periods of six hours varied from more than twenty grams in the case of isobutylmagnesium bromide to less than six grams in the case of ethylmagnesium bromide.

Effect of heat on the reaction. One mole of propylene oxide was added to one mole of ethylmagnesium bromide cooled in ice. Half of the ether was distilled off and replaced with

TABLE II
DERIVATIVES OF THE ALCOHOLS AND CORRESPONDING KETONES

ALCOHOL	DERIVATIVES	M. P. °C	% N' CALCD	% N FOUND
1-Bromo-2-propanol (9) B.p. 49.6° (12 mm.); n_D^{20} , 1.4801	3,5-Dinitrobenzoate (9) α -Naphthylurethan 2,4-Dinitrophenylhydrazone	85-87 116-116.5 128	4.54 17.66	4.33 17.56
2-Pentanol (5) B.p. 118.8° (745 mm.); n_D^{20} , 1.4068	3,5-Dinitrobenzoate (5) α -Naphthylurethan (10) 2,4-Dinitrophenylhydrazone(10)	59-61 75 143-145*		
2-Hexanol (15) B.p. 139.5° (740 mm.); n_D^{20} , 1.4155	3,5-Dinitrobenzoate (11) 2,4-Dinitrophenylhydrazone (10)	36-37 106-108*		
4-Methyl-2-pentanol (10) B.p. 68° (52 mm.); n_D^{20} , 1.4120	3,5-Dinitrobenzoate (11) α -Naphthylurethan (4) 2,4-Dinitrophenylhydrazone(10)	61-62 94-95.5 91-92*	5.16	4.96
2-Heptanol (10) B.p. 77° (24 mm.); n_D^{20} , 1.4214	3,5-Dinitrobenzoate (10) 2,4-Dinitrophenylhydrazone	47.5-48.5 72.5-73.5*		
4-Methyl-2-hexanol (12) B.p. 85.5° (44 mm.); n_D^{20} , 1.4223	3,5-Dinitrobenzoate (12) Semicarbazone (12)	62.5-63.5 128-129*	9.03	9.09
5-Methyl-2-hexanol (16) B.p. 73° (32 mm.); n_D^{20} , 1.4227	3,5-Dinitrobenzoate 2,4-Dinitrophenylhydrazone (10)	34-36 94-96	9.03	8.97
4,4-Dimethyl-2-pentanol (13) B.p. 65° (40 mm.); n_D^{20} , 1.4248	3,5-Dinitrobenzoate (13)	48-50		
1-Phenyl-2-propanol (10, 14) B.p. 95° (7 mm.); n_D^{20} , 1.5221	α -Naphthylurethan (14) Semicarbazone (10)	88-89.8 193		
1-Mesityl-2-propanol B.p. 137° (9 mm.); n_D^{20} , 1.5282	3,5-Dinitrobenzoate α -Naphthylurethan Semicarbazone	153.8-154.8 114.8-115.2 206-206.5	7.42 3.97	7.36 3.84

* Checked by a mixed m.p. with a known derivative.

benzene. The mixture was refluxed for six hours and then allowed to stand overnight. Decomposition with saturated ammonium bromide and analysis indicated a yield of fourteen grams of 1-bromo-2-propanol (10%). Distillation of the ether-benzene solution gave a fraction of twenty grams between 100° and 120°. Refraction of this gave seven grams at 100-104° (40%) and eleven grams at 117-120° (60%). The 100-104° fraction was identified by its boiling point, density, refractive index, and α -naphthylurethan as 2-methyl-2-butanol. The 117-120° fraction was identified as 2-pentanol.

Derivatives. The 3,5-dinitrobenzoates were made by using pyridine and 3,5-dinitrobenzoyl chloride. Another method was developed for any type of alcohol (primary, secondary, or tertiary) or phenol which made use of ethylmagnesium bromide. The alcohol must not contain any contaminant that forms an alcoholate with Grignard reagent. After the slight excess of alcohol had been added to the cooled Grignard reagent (evolution of ethane ceased), 0.5-1 g. of 3,5-dinitrobenzoyl chloride was added. The tube was stoppered with a calcium chloride tube and allowed to stand overnight or longer if the alcoholate was slow in reacting. Water was added to precipitate the magnesium salts and the ether layer filtered off and evaporated.

α -Naphthylurethans were prepared from α -naphthyl isocyanate using a drop of trimethylamine-ether solution as catalyst.

As further proof, the secondary alcohols were oxidized to ketones with a saturated solution of KMnO_4 in 1 to 6 N H_2SO_4 and filtered. The 2,4-dinitrophenylhydrazones were made by adding this filtrate to three ml. of a solution of 2.4 g. of 2,4-dinitrophenylhydrazine in a mixture of 80 ml. of water and 40 ml. of 72% perchloric acid. The semicarbazones were made by separating the ketone from the water and using the method for water-insoluble ketones.

Preparation of magnesium bromide etherate and reaction with propylene oxide. Twenty-nine grams of magnesium was placed in the reaction flask and covered with 500 ml. of ether. One hundred sixty grams (26 ml.) of bromine was added dropwise. After all of the bromine had been added, the reaction mixture was refluxed for an hour and allowed to stand overnight. The magnesium bromide solution was removed from the excess magnesium, measured, and titrated for bromide ion. The reaction with 2 moles of propylene oxide was carried out in the same manner as with the Grignard reagent.

Two hours after addition of all the epoxide, the precipitate was placed in centrifuge bottles, stirred with anhydrous ether, and centrifuged. The ether layer was decanted and the process of washing repeated. The precipitate was dried in a vacuum desiccator over calcium chloride for several days at 12 mm. or less. The amount of bromine was determined by the Parr bomb method.

Anal. Calc'd for $\text{C}_6\text{H}_6\text{Br}_2\text{MgO}_2$: Br, 53.2; Mg, 8.1.

Found: Br, 51.7; Mg, 8.5.

Reaction of diethylmagnesium with two mole equivalents of bromohydrin. The calculated amount of bromohydrin was mixed with 200 ml. of benzene, placed in the reaction flask, and cooled. The diethylmagnesium solution (8) was added from the dropping-funnel. The resulting white solid (which formed immediately) was washed with ether by centrifuging and dried in a vacuum desiccator under reduced pressure.

Anal. Calc'd for $\text{C}_6\text{H}_6\text{Br}_2\text{MgO}_2$: Br, 53.2; Mg, 8.1.

Found: Br, 51.2; Mg, 8.5.

Reaction of diethylmagnesium with one mole equivalent of bromohydrin. The diethylmagnesium solution was placed in the reaction flask and the bromohydrin, mixed with an equal volume of benzene, was added slowly. A white precipitate formed. The reaction mixture was allowed to stand four days, refluxed six hours, and hydrolyzed. Part of the bromohydrin was recovered along with some alcohol. On oxidation, the alcohol gave 2-pentanone which was checked by a mixed melting point of its 2,4-dinitrophenylhydrazone with a known derivative.

SUMMARY

1. When one mole of propylene oxide was added to one mole of alkylmagnesium bromide, both alkylmagnesium bonds and magnesium bromine bonds reacted but the reaction was predominantly with the magnesium bromine bonds. The yield of secondary alcohol was small as compared with that of propylene bromohydrin. When one mole of propylene oxide was added to one mole of aryl-

magnesium bromide, the addition was predominantly at the arylmagnesium bond and the yield of alcohol exceeded slightly that of the bromohydrin.

2. The addition of a second mole of propylene oxide to alkylmagnesium bromide (excepting isobutylmagnesium bromide and *tert.*-butylmagnesium bromide) gave a slight increase in the yield of bromohydrin. In all cases, addition to the alkylmagnesium bond occurred. This addition was relatively slow, the rate depending upon the size of the alkyl group and branching. The yields of secondary alcohols from normal primary alkyl bromides were more than 50%; from secondary alkyl bromides, more than 30%; and from isobutyl and *tert.*-butyl bromides, 15%.

3. Refluxing the reaction mixture from ethylmagnesium bromide and propylene oxide at the boiling temperature of benzene, caused partial decomposition of the intermediates with the formation of acetone and 2-methyl-2-butanol. That this type of decomposition and rearrangement takes place to some extent at room temperatures or below was evidenced by the presence of small amounts of acetone in all reaction mixtures.

EAST LANSING, MICH.

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1,9-CYCLOHEXYLENEFLUORENE, A PENTACYCLIC RING SYSTEM

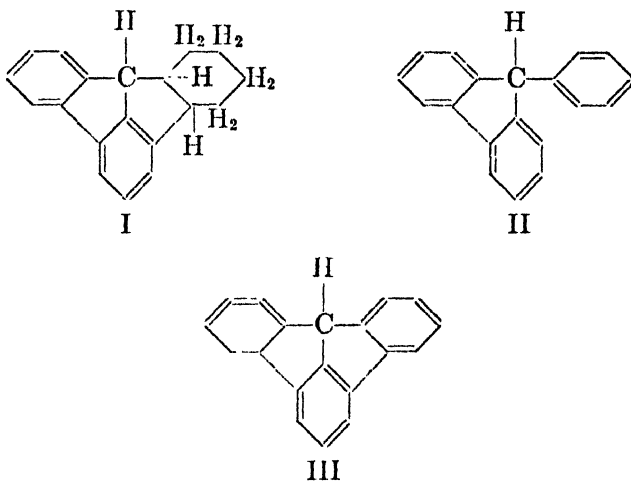
CHARLES D. HURD AND JAMES D. MOLD¹*Received August 15, 1947*

The present paper describes the synthesis of 1,9-cyclohexylenefluorene (I), which represents a new pentacyclic ring system. Dehydrogenation of this hydrocarbon gave rise to 9-phenylfluorene (II) instead of the expected 1,9-*o*-phenylene-fluorene (III).

The first approach to the synthesis of III was by pyrolysis of 9-chloro-9-phenylfluorene at 260–270°. Hydrogen chloride was evolved, but III was not isolated. Instead, a dimeric product was formed in good yield. The equation:



may account for the change but present evidence is not conclusive. Molecular weight determinations were reasonably satisfactory but the carbon analysis was low. The latter may be caused by difficulty in obtaining complete combustion because, on burning, the substance leaves a non-oxidizable carbonaceous residue.

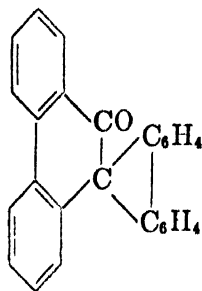


This pyrolytic reaction was patterned after the known decomposition (1) of triphenylmethyl chloride, $(C_6H_5)_3CCl$, into II. In view of the conflicting reports in the literature regarding conditions for this pyrolysis, a study of it was undertaken, preceding the experiments mentioned above. The various conditions reported in the literature were duplicated. In addition, runs were carried out in solvents (Halowax and quinoline), or by distilling through a heated Pyrex tube, or by heating triphenylmethyl chloride vapors at 700°; but it never was possible to isolate 9-phenylfluorene in a yield greater than 10%. Yields up to 26% of

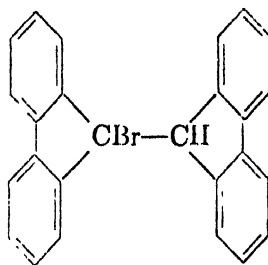
¹ duPont Fellow, 1943–1944. Present address: Parke, Davis and Company, Detroit, Michigan.

triphenylmethane were obtained in some cases. Pyrolysis of triphenylmethyl acetate was tried also. Although acetic acid was evolved, the products consisted of triphenylmethane and higher condensation products, but no 9-phenylfluorene was isolated.

Since the pyrolytic synthesis of III was not satisfactory, a chemical synthesis of I was undertaken, the procedure being patterned after the synthesis of phenanthrene as carried out by Bardhan and Sengupta (2). This involved as the first step the synthesis of ethyl 2-cyclohexanonecarboxylate, by the condensation of cyclohexanone and ethyl oxalate (3). In the next step 9-chlorofluorene was prepared. For this purpose fluorene was first oxidized to fluorenone. Hydrogenation of the latter with nickel gave 61% yields of fluorenol, whereas reduction by sodium and alcohol yielded only a syrup. Fluorenol was converted in nearly quantitative yield into chlorofluorene by interaction with concentrated hydrochloric acid. The corresponding bromide was prepared in good yield also from fluorenol and hydrobromic acid, and in 40% yield by the use of a solution of dry hydrogen bromide in glacial acetic acid (4) at room temperature; but curiously, quite different results were obtained when a solution of hydrogen bromide in hot glacial acetic acid was used. Evidently the temperature at which this reaction is carried out has a considerable influence in determining its course. In the latter reaction the two chief products were 10,10-diphenylnephenanthrone (IV) and a crystalline bromide which seemed to be 9-bromo-9-(9'-fluorenyl)fluorene (V) contaminated with a hydrocarbon, presumably bisdiphenyleneethane or bisdiphenyleneethylene. Some fluorene was isolated also.

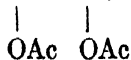


IV



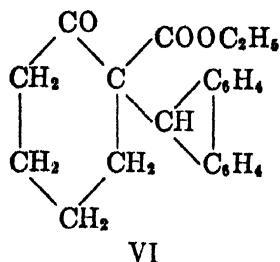
V

Compound IV is known, but V is new. Klinger and Lonnes (5) identified IV as a product from the reaction of bisdiphenyleneethylene acetate, $(C_6H_5)_2C-C(C_6H_5)_2$, with 70% sulfuric acid at 100°. This compound is also



identical with that isolated by Graebe and Stindt (6) from the hydrolysis of bisdiphenyleneethylene bromide at 150°.

Ethyl 2-fluorenyl-2-cyclohexanonecarboxylate (VI) was synthesized by condensation of 9-chlorofluorene and ethyl potassio-2-cyclohexanonecarboxylate.



Saponification of this ester gave rise to 2-fluorenylcyclohexanone, which was hydrogenated catalytically to 2-fluorenylcyclohexanol. The sodium reduction of this ketone was less satisfactory, much of the ketone being unchanged. Furthermore, the phenylurethans of the alcohols prepared by the two methods melted at different temperatures. Since there are two asymmetric centers in the alcohol, it is possible that one racemic mixture was obtained from the sodium reduction and the other racemic mixture from the catalytic reduction.

Cyclodehydration of 2-fluorenylcyclohexanol to 1,9-cyclohexylenefluorene (I) was accomplished in 60% yield by the use of syrupy phosphoric acid (7). Phosphorus pentoxide (8) gave far smaller yields of crystalline product, the chief substance formed being a syrup which absorbed bromine to give an impure green-black solid. Sulfuric acid was tried also, but difficulties of sulfonation were encountered. Attempts to hydrolyze the sulfonic acids produced were ineffective, although similar hydrolytic experiments carried out with fluorenesulfonic acids did give fluorene in good yield. The 1,9-cyclohexylenefluorene was a colorless solid which melted at 111.5–112°.

As was mentioned earlier, dehydrogenation of I gave rise to 9-phenylfluorene. This was produced in excellent yields by treatment with palladium-charcoal catalyst in a refluxing solution of *p*-cymene, and in lower yields by use of selenium at 280–290°. Since the production of phenylfluorene from I involves an unusual carbon-to-carbon cleavage it becomes necessary to prove that neither cyclohexenylfluorene nor cyclohexylfluorene were produced from 2-fluorenylcyclohexanol by reaction with phosphoric acid. Cyclohexenylfluorene may be dismissed from consideration since the hydrocarbon was inert towards bromine and towards potassium permanganate, pointing to its essentially saturated nature. Cyclohexylfluorene was eliminated since it is known (18) to melt at 102–103°. Furthermore, since the C,H percentages in $C_{19}H_{18}$ and $C_{19}H_{20}$ differ by 0.76, combustion data also are sufficient for a decision. The data were very satisfactory for $C_{19}H_{18}$.

EXPERIMENTAL

All melting points and boiling points are corrected.

Pyrolysis of triphenylmethyl acetate. Pyrolysis of 5 g. of triphenylmethyl acetate (9) in a 5-cc. distilling flask for eighty minutes at 250° and 35–45 mm. yielded 1.0 g. of crude triphenylmethane (isolated by slow evaporation of a benzene solution of the product) and 1.2 g. of an unknown tan solid. The latter crystallized from xylene-butanol in pale yellow

crystals (*Anal.*: C, 93.21; H, 5.34) which did not melt below 280°. On burning, the material formed a persistent carbonaceous residue.

9-Chloro-9-phenylfluorene. 9-Phenyl-9-fluorenol was synthesized (10) and from it 9-chloro-9-phenylfluorene, m.p. 78–79°, was prepared by interaction with acetyl chloride.

For this synthesis, 5 g. of the fluorenol was dissolved in 10 g. of acetyl chloride and the mixture was poured into 20 ml. of concentrated hydrochloric acid. The yellow oil which separated soon solidified; m.p. 78–79°. The yield was nearly quantitative.

Pyrolysis. No change in the 9-chloro-9-phenylfluorene was apparent below 250° but at higher temperatures (250–290°) hydrogen chloride was evolved. Heating of 5 g. of it was continued for three hours, after which the cooled material was extracted with hot benzene, from which 4 g. of solid was precipitated by addition of hexane. The solid was insoluble in hot alcohol or ether but was crystallized (pink crystals) from xylene. The crystals did not melt below 280°. On burning, the substance left a non-oxidizable carbonaceous residue. A qualitative test for halogen was negative.

Anal. Calc'd for $C_{23}H_{24}$: C, 94.98; H, 5.02; molec. wt., 480.

Found: C, 91.57; H, 5.63; molec. wt. 468.

9-Fluorenol. Fluorenone (11), 53.6 g., was dissolved in 100 ml. of absolute ethyl alcohol and 5.5 g. of powdered nickel on kieselguhr catalyst (Victor Chemical Co.) was added. A 450-ml. bomb was employed and was charged with 115 atm. of hydrogen. The temperature was maintained at 70–75° and the theoretical amount of hydrogen was absorbed after four hours. A crude yield of 33.9 g. (63%) of fluorenol, m.p. 151–154°, was obtained by crystallization from the solvent. This was purified by recrystallizing from benzene to give 32.8 g. (61%) of product which melted at 153–154° (lit. 156°).

9-Chlorofluorene. An almost quantitative yield was obtained by allowing 33.0 g. of fluorenol to stand with 190 ml. of concentrated hydrochloric acid for twenty-four hours with intermittent shaking. The 9-chlorofluorene was filtered, washed with aqueous alcohol and dried, m.p. 91° (lit. 91°).

9-Bromofluorene. A. A sample of fluorenol (4.14 g.) was allowed to stand with intermittent shaking with 41 ml. of 41% hydrobromic acid for thirty-six hours. At the end of this time, the solid material was filtered off, washed with aqueous ethanol and dried to give 5.02 g., m.p. 99–101°. Several crystallizations from 95% ethanol yielded 3.72 g. (65%) of product, m.p. 104°. The remainder of the material melted over the range 125–130° and was probably a mixture of fluorenol and 9-bromofluorene. Undoubtedly, better yields could be obtained by more careful control of the conditions.

B. A sample of fluorenol (0.32 g.) was dissolved in 10 ml. of glacial acetic acid. Twice the equimolar amount of dry hydrogen bromide, generated by dropping bromine into refluxing tetralin, was passed into a second 10-ml. portion of glacial acetic acid. These two solutions were mixed at room temperature and most of the solvent removed *in vacuo* after the mixture had stood for a few minutes. Crystals formed upon the addition of a small small volume of pentane. A 40% yield (0.17 g.) of 9-bromofluorene, m.p. 103–104°, was obtained in addition to impure fluorenol.

C. Fluorenol (32.78 g.) was dissolved in 250 ml. of glacial acetic acid warmed upon the steam-bath. Dry hydrogen bromide was bubbled into the warm solution for two hours, at which time the solution had become a deep amber color. On cooling, a pale yellow crystalline solid separated which turned brown at 160° and melted at 218°. Recrystallization from benzene gave white crystals which melted at 257–258°. Further crystallizations led to the isolation of 7.5 g. of 10,10-diphenylenephenanthrene (IV), m.p. 256–258°; 11 g. of an impure fraction, turning red at about 190° and melting to a red liquid with the evolution of gas; and 8.5 g. of red-brown syrup of sharp odor. One gram of fluorene, m.p. 114°, was separated from the last by distillation.

The identification of 10,10-diphenylenephenanthrene was accomplished by heating for a short time with alcoholic sodium ethoxide followed by acidification to yield 2-(*o*-fluorenyl-phenyl)benzoic acid (5), m.p. 240–242° (lit. 242°), neutral equivalent 364 (theoret. 362).

The 11-g. fraction was identified as chiefly 9-bromo-9-(9'-fluorenyl)fluorene (V) by halo-

gen analysis, by reduction, and by treatment with alcoholic potash. The halogen determination was carried out according to the directions of Umhoefer (12). (Calc'd: Br, 19.6. Found: Br, 17.6.) A 0.5-g. sample was refluxed for two hours with 1.0 g. of zinc dust and 25 ml. of benzene. Two fractions of crystals were obtained, one of which was pale yellow and melted at 224–225°, apparently the purified starting material. The other fraction was orange and melted over a range of 160–180°. Recrystallization from 95% ethanol led to a few beautifully formed red crystals, m.p. 173–174°. A molecular weight determination on the material melting at 160–180° indicated a molecular weight of 327. Bis(diphenylene)ethene (5, 6) has the molecular weight 328 and is a red solid, m.p. 189–190°. Contamination with bis(diphenylene)ethane would lower the melting point and fade the color but would only change the molecular weight by two units.

Another sample of the 11-g. fraction (0.2 g.) was dissolved in 20 ml. of a 10% ethanolic potassium hydroxide solution, and the mixture was refluxed for three hours. Addition of water to the resulting red solution gave a brick red precipitate melting below 150° and containing no halogen. Upon acidification of the filtrate, a yellow solid precipitated which was purified by crystallization from xylene, m.p. 241.5–242°. This was believed to be bis(diphenylene)ethane, lit. m.p. 242, 244° (6, 13, 18).

Ethyl 2-fluorenyl-2-cyclohexanonecarboxylate (VI). The procedure followed was patterned after a similar preparation carried out by Bardhan and Sengupta (2). Ethyl 2-cyclohexanonecarboxylate, b.p. 109° (13 mm.), was prepared in 35% yield by the method of Kotz and Michels (3), starting with cyclohexanone and ethyl oxalate. Potassium (0.90 g., 0.033 mole) was powdered under xylene, the latter replaced by dry benzene and 3.80 g. (0.023 mole) of ethyl 2-cyclohexanonecarboxylate was added. The solution became warm, the potassium melted and a yellow precipitate settled out as the solution turned red in color. A benzene solution of 9-chlorofluorene was added and the volume brought to about 40 ml. with additional benzene. Refluxing was carried out over a period of twenty-four hours, after which the solution was cooled, washed with water, dried with sodium sulfate and the benzene evaporated *in vacuo*. Crystallization was accomplished by dissolving the residue in a small amount of benzene and adding an excess of ligroin. A 35% yield of white crystalline material, m.p. 133.0–133.5°, was obtained. In later preparations it was found that fractional crystallization from glacial acetic acid served well to separate the product from unreacted starting material.

Anal. Calc'd for $C_{22}H_{22}O_2$: C, 79.01; H, 6.63.

Found: C, 79.10; H, 6.64.

Oxime. This derivative was prepared readily by refluxing the keto ester with hydroxylamine hydrochloride in pyridine and ethanol (14a). Purification was accomplished by several crystallizations from 95% ethanol, m.p. 170.5°.

Anal. Calc'd for $C_{22}H_{23}NO_2$: N, 4.01. Found: N, 3.86.

2-Fluorenylcyclohexanone. Five grams of the keto ester (VI) was dissolved in 50 ml. of 95% ethanol containing 5.0 g. of potassium hydroxide. This solution was refluxed on the steam-bath for twenty-two hours. At first a rather vigorous foaming was noted, then the solution became pale yellow in color and some white solid precipitated at the sides. This dissolved upon the addition of 25–30 ml. of water, leaving a few ml. of darker liquid layer at the bottom. The solvents were removed *in vacuo* at room temperature and a white amorphous solid separated. Hydrochloric acid was added to acidity, and the white solid seemed to dissolve with the evolution of considerable gas and the formation of a different, white insoluble compound which gave a yellow oil upon short heating. This mixture was extracted with ether, dried over sodium sulfate, and the ether evaporated to give a viscous amber liquid. Crystallization from aqueous alcohol gave 1.40 g. of white solid, m.p. 112.5–113.5°.

Anal. Calc'd for $C_{19}H_{18}O$: C, 87.00; H, 6.92.

Found: C, 86.99; H, 6.86.

Semicarbazone. The residual syrup was treated with semicarbazide hydrochloride (14b) and 0.89 g. of the semicarbazone, m.p. 220°, was obtained.

Anal. Calc'd for $C_{20}H_{21}N_3O$: N, 13.15. Found: N, 12.77.

The ketone was regenerated by heating for eight hours on the steam-bath with 6 *N* hydrochloric acid. The mixture was filtered, washed with water, dried, and recrystallized from aqueous alcohol to give an 87% yield of silvery-white platelets, m.p. 112.5–113.5°.

2-Fluorenylcyclohexanol. A. Sodium in moist ether was used in an attempt to reduce the above ketone to the corresponding alcohol, but the small amount of product which was obtained could not be purified readily. It apparently contained chiefly the ketone (identified as the semicarbazone) as well as some alcohol, which was indicated by the preparation of its phenylurethan, m.p. 167.5–168.5°.

Anal. Calc'd for $C_{26}H_{25}NO_2$: C, 81.40; H, 6.57.

Found: C, 80.84; H, 6.35.

B. A 1.31-g. (0.0034 mole) sample of the ketone was dissolved in 20 ml. of dioxane (purified by refluxing over hydrochloric acid and distilling from sodium). This solution was placed in a 43-ml. bomb together with 0.5 g. of copper chromium oxide catalyst (15). The bomb was charged with 1330 lbs. of hydrogen and the temperature maintained at 150°. The theoretical amount of hydrogen was absorbed after one and three-quarters hours. The catalyst was removed by centrifuging and the solvent evaporated. The residue was crystallized from 95% ethanol to give 1.11 g. (85%) of beautiful flat stellate clusters of crystals, m.p. 122.0–122.5°.

Anal. Calc'd for $C_{19}H_{20}O$: C, 86.38; H, 7.58.

Found: C, 86.32; H, 7.36.

The phenylurethan of this alcohol was prepared, m.p. 144.5–145.5° (14c). A mixed melting point with the isomeric phenylurethan from the reduction by sodium and moist ether (m.p. 167.5–168.5°) caused a lowering of 20°.

Anal. Calc'd for $C_{27}H_{25}NO_2$: C, 81.40; H, 6.57.

Found: C, 80.93; H, 6.53.

Cyclodehydration of 2-fluorenylcyclohexanol. With phosphorus pentoxide. A 0.1-g. sample of the alcohol (m.p. 120–121°) prepared above by catalytic reduction was heated with 0.2 g. of phosphorus pentoxide in a 10-ml. distilling flask for twenty minutes at 135–140° and 17 mm. of mercury. The temperature was then raised to 170° and maintained for ten minutes (8); the reaction mixture was cooled and water was added with cooling. The mixture was extracted with ether, the extract dried with potassium carbonate, the ether evaporated, and the residue crystallized from alcohol-ether solution by allowing the ether to evaporate. A very small amount of white crystalline material was obtained, m.p. 101–105°, which did not absorb bromine and was unreactive toward potassium permanganate. The major portion of product was an amber syrup which absorbed bromine to give an impure green-black solid.

With concentrated sulfuric acid. To 7 ml. of 90% sulfuric acid was added 0.1 g. of the alcohol over a period of one hour at a temperature of 3–5°. The solution turned a deep rose-violet color, and was removed from the ice-bath and allowed to stand two more hours at room temperature. The solution was then diluted with 60 ml. of ice-water, and a yellow solid precipitated. The physical properties of this solid indicated the presence of a sulfonic acid grouping. Sodium fusion followed by treatment with lead chloride solution gave a black precipitate indicating the presence of sulfur. An attempt to remove the sulfonic acid group by heating with 37% hydrochloric acid in a sealed tube at 200° for twenty-four hours met with failure, although similar treatment sufficed to hydrolyze the sulfonic acid of fluorene in 60% yield.

With syrupy phosphoric acid (7). Twenty ml. of 85% phosphoric acid was distilled up to 230° in a 25-ml. distilling flask. At this point, 0.5 g. of 2-fluorenylcyclohexanol was added and heating continued for one-half hour. The solution was cooled, diluted with water, and extracted several times with benzene. The benzene extract was dried over potassium carbonate, filtered, the filtrate evaporated to dryness, and the residue crystallized from 95% ethanol to yield 0.30 g. of crude product. Further recrystallization led to 0.22 g., m.p. 109–110°, a 44% yield of I. Crystallization by cooling a hot methanol solution of the compound

gave beautiful large needles, m.p. 111.5–112.0°. This material did not add bromine and was inert towards alkaline permanganate solution.

Anal. Calc'd for $C_{19}H_{18}$: C, 92.64; H, 7.36.

Found: C, 92.53; H, 7.37.

Dehydrogenation. A. The dehydrogenation of (I) was accomplished by refluxing a solution containing 80 mg. of it in 2 ml. of *p*-cymene with 5% palladium-charcoal catalyst (16). The surface was swept with carbon dioxide during the reaction, and the hydrogen was collected and measured over 50% potassium hydroxide solution. Fresh portions of catalyst were added at intervals to accelerate the reaction. At the conclusion of the reaction the catalyst was filtered off and the filtrate was concentrated by vacuum distillation. Crystallization was induced by the addition of methanol with cooling. An almost quantitative yield of product, m.p. 137–142°, was obtained. Recrystallization from methanol produced fine colorless needles of 9-phenylfluorene, m.p. (and mixed m.p.) 146.5–147°.

Anal. Calc'd for $C_{19}H_{14}$: C, 94.17; H, 5.82.

Found: C, 94.55; H, 5.80.

B. The dehydrogenation of (I) was also accomplished by heating 0.1 g. of the hydrocarbon in a 25-ml. flask with 0.3 g. of selenium at 280–290° for twenty-one hours in a Wood's metal-bath (17); the reaction mixture was cooled and extracted with benzene. After removal of the benzene, the residue was crystallized from aqueous ethanol to give a first crop of 0.03 g., m.p. 137–139°, and a second crop of 0.103 g., m.p. 120–125°. Purification was accomplished by several further crystallizations from aqueous ethanol and a final crystallization from methanol, giving the fine white needles of 9-phenylfluorene, m.p. 142.5–144°.

ACKNOWLEDGMENTS

Micro combustion and micro Dumas analyses were performed by T. S. Ma and Patricia Craig.

SUMMARY

Pyrolysis of triphenylmethyl chloride was carried out under various conditions with no improvement in yield of 9-phenylfluorene over those reported by previous workers. Under similar conditions, pyrolysis of triphenylmethyl acetate yielded triphenylmethane and higher condensation products.

Pyrolysis of 9-chloro-9-phenylfluorene gave rise to good yields of higher dimeric products but no 1,9-*o*-phenylenefluorene.

The synthesis of 1,9-cyclohexylenefluorene was accomplished. Dehydrogenation methods convert this substance into 9-phenylfluorene.

EVANSTON, ILLINOIS

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ISATOIC ANHYDRIDE. II. REACTIONS OF ISATOIC ANHYDRIDE WITH AMMONIA

ROGER P. STAIGER AND E. C. WAGNER

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Reactions of isatoic anhydride with primary and secondary amines (1) in general yield either the corresponding *o*-aminobenzamides or, by continued reaction of isatoic anhydride with the amino group exposed by each such condensation, the so-called "abnormal" products shown to be mixtures of polyanthranoylanthranilamides, in both cases with loss of carbon dioxide. Ammonia and isatoic anhydride have long been known to yield anthranilamide (2), but Sheibley (3) reported that action of hot ammonia-water on dihalogenoisatoic anhydrides yielded none of the corresponding dihalogenoanthranilamide but only dihalogenobenzoylene urea and dihalogenoanthranilic acid, and represented the results by the equation: $5 \text{ di-X-isatoic anhydride} + 2\text{NH}_3 + \text{H}_2\text{O} \rightarrow 2 \text{ di-X-benzoylene urea} + 3 \text{ di-X-anthranilic acid} + 3\text{CO}_2$. Using ethylamine instead of ammonia Sheibley obtained results only partially analogous, the products being the corresponding benzoylene urea and the substituted anthranilamide. The formation of benzoylene ureas, which was not observed by Clark and Wagner during reactions of isatoic anhydride and amines,¹ indicates that the reactions can follow another course which leads to ring-closure without loss of carbon dioxide. This paper reports the findings of a study to seek an explanation for the seemingly conflicting claims outlined above, and especially to learn the course by which benzoylene ureas are formed. The simplest case, that of isatoic anhydride and ammonia, was selected for examination; other cases will be studied later.

Comparison of the experimental conditions used by Clark and Wagner and those used by Sheibley reveal that the former took the reactants generally in about equivalent amounts but that Sheibley used both ammonia (as strong ammonia water) and ethylamine in enormous initial excess.²

Experiments to test the importance of this difference in conditions showed that the proportions of isatoic anhydride and ammonia, and the concentration of the latter, are factors which determine the proportions of two obtainable products,

¹ Benzoylene urea was obtained by interaction of isatoic anhydride with ethyl carbamate and with urea, as a result of expected reactions. Otherwise no search was made for benzoylene urea in the reaction mixtures.

² Clark and Wagner used amine in large excess only when the 1:1 ratio yielded "abnormal" products, indicating presumably an unfavorable ratio of the speeds of the normal and "abnormal" reactions. This was the case with some primary aromatic amines and five of the seven secondary amines tested. By use of amine in large excess the disadvantage mentioned was overcome to some extent in the case of *p*-bromoaniline and to greater extents with the secondary amines, showing that large excesses of these amines present throughout the reactions operated to decrease the incidence of the "abnormal" reaction. The failure of secondary amines to yield benzoylene ureas by this procedure has no bearing on the inquiry, for secondary amines are clearly incapable of providing a nitrogen atom for the diazine ring of benzoylene urea.

viz., anthranilamide and benzoylene urea. Using ammonia in amount and concentration near the minima required for involvement of all the isatoic anhydride (2.5 equivalents of ammonia at 1-molar concentration) there resulted no benzoylene urea but only anthranilamide amounting to over 90% of the theoretical yield. Benzoylene urea first appeared as a product (10%) with 5 equivalents of ammonia at 2-molar concentration, and was accompanied by 90% of anthranilamide. As the concentration and excess of ammonia were increased the yields of benzoylene urea increased steadily to a maximum of about 42% (40 equivalents of ammonia at 16-molar concentration), while those of amide decreased to 55%. The data for these experiments appear in Table I, the significant features of which are immediately obvious in Figure 1.

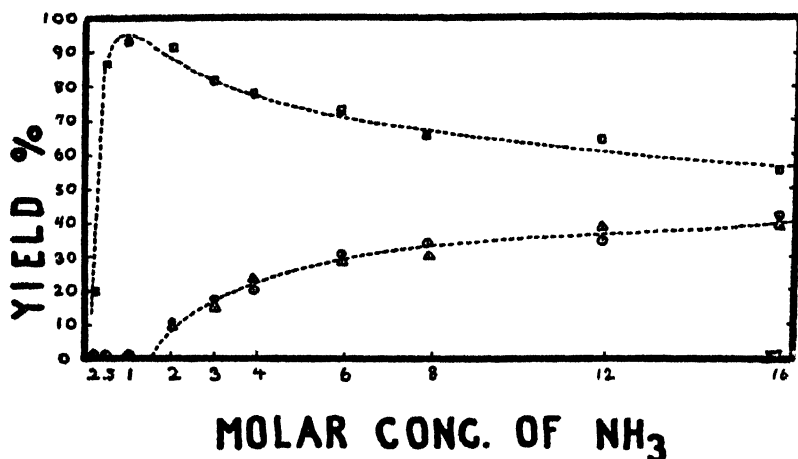
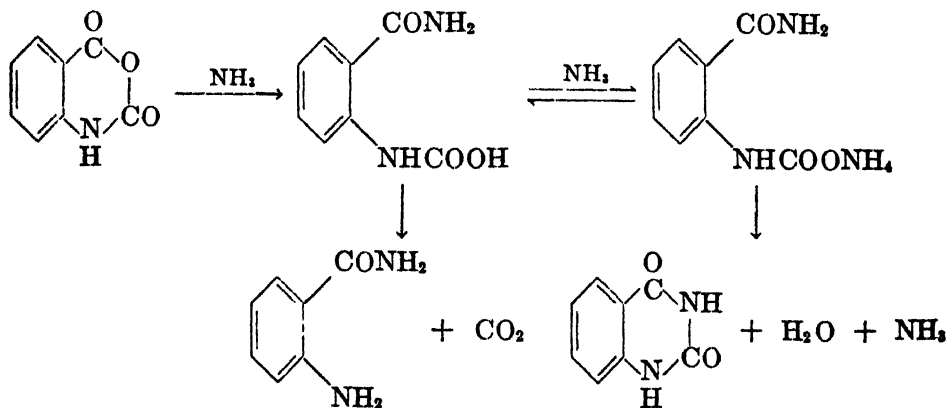


FIG. 1. INTERACTION OF ISATOIC ANHYDRIDE AND AMMONIA

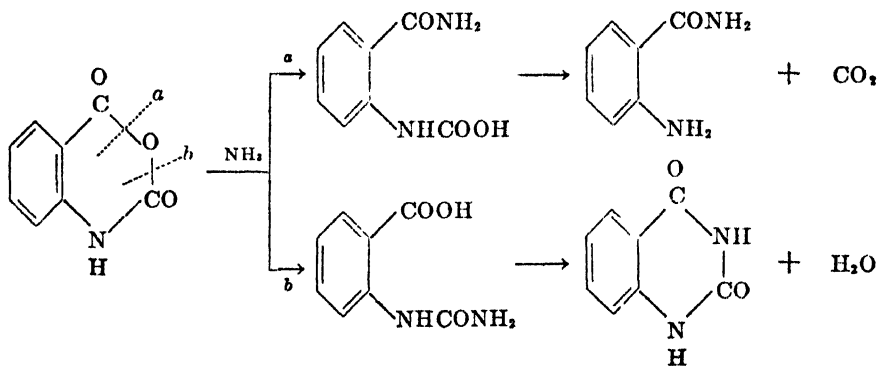
□ anthranilamide
 △ uramido benzoic acid
 ○ benzoylene urea

It was conjectured at first that the effect of high concentration of ammonia in favoring the formation of benzoylene urea might be a stabilization of isatoic acid as its ammonium salt, sufficient to delay decarboxylation and permit ring closure:



This view proved untenable, for experiments to test it by use of large amounts of added ammonium salt yielded the result that with the liquid nearly saturated with ammonium acetate no benzoylene urea was found at any concentration of ammonia from 4-molar to 12-molar, at which concentrations but in absence of ammonium acetate the yields of benzoylene urea are 20% and 40% respectively. In the presence of ammonium acetate, the isolable product was anthranilamide in high yield.

The surmise was then tested that two separate and competitive reactions lead to formation of anthranilamide and of benzoylene urea, involving two different cleavages of the mixed anhydride grouping of isatoic anhydride (see reaction scheme below). This proved to be correct, for under conditions known to yield benzoylene urea it was found that, after the initial reaction with ammonia in large excess, acidification of the chilled mixture caused the separation of a compound identified as *o*-uramidobenzoic acid, which is the primary product to be expected by cleavage at *b* (reaction scheme), and which is convertible with the greatest ease to benzoylene urea (4). It is significant that the amounts of uramidobenzoic acid (determined in separate experiments) paralleled closely those of benzoylene urea at all concentrations of ammonia (Figure 1), leaving little reason to doubt that uramidobenzoic acid is the precursor of benzoylene urea. The filtrates always contained anthranilamide in quantity, but no anthranilic acid formed by hydrolysis of anthranilamide, which in separate tests was found to be apparently unaffected by concentrated ammonia water at room temperature. Experiments to test the effects of temperature and time, with the concentration of ammonia constant, showed clearly that the determining variable is the concentration of ammonia. The two reactions appear to be independent except as both consume isatoic anhydride. The interaction of isatoic anhydride and ammonia may be represented as shown in the reaction scheme:



For the present there is withheld speculation as to the reason why cleavage of isatoic anhydride at *b* requires a higher concentration of ammonia than cleavage at *a*. In the experiments there was found no "abnormal" product (formed by condensation of anthranilamide with isatoic anhydride), indicating that the action of ammonia was so rapid as to exclude this secondary condensation. The "abnormal" reaction appeared to occur when isatoic anhydride was treated with only one-half equivalent of ammonia, the product being an amorphous material

similar to that reported previously (5) as formed from anthranilamide and isatoic anhydride.

These findings for the interaction of isatoic anhydride and ammonia parallel Sheibley's findings for reactions of dihalogenoisatoic anhydrides with ethylamine but not with ammonia. It may be suspected that Sheibley's equation for the interaction of ammonia and dihalogenoisatoic anhydrides represents a composite of several concurrent reactions and that the stoichiometric relationships on which it is based are valid in an over-all sense for the somewhat indefinite conditions used, *viz.*, concentrated aqueous ammonia in large initial excess which decreased rapidly as the mixture was heated.

EXPERIMENTAL

Action of aqueous ammonia on isatoic anhydride. General procedure. In the experiments represented in Table I, 1.63 g. (0.01 mole) of powdered isatoic anhydride was added with stirring to 25 ml. of water containing ammonia in concentrations from 0 to 16 molar, corresponding to molar ratios (with respect to isatoic anhydride) of 0 to 40, and obtained by diluting the requisite concentrated aqueous ammonia with water as required. Reaction was allowed to occur at room temperature (about 23°); the negligible effect of temperature upon the essential results is shown later. When the concentration of ammonia was molar or greater the isatoic anhydride dissolved more or less promptly. The solution was then examined for anthranilamide and for either uramidobenzoic acid or benzoylene urea by the procedure outlined below; the negligible effect of reaction time upon the essential results is shown later. When the concentration of ammonia was (or became) 0.4 molar or less the isatoic anhydride did not dissolve completely. In such cases the suspension was stirred at regular intervals during periods of six hours or more, and the mixture was examined by the procedure given below.

Procedure for analysis of reaction mixtures. If isatoic anhydride did not dissolve completely after about six hours the mixture was filtered through a tared Gooch crucible, and the collected isatoic anhydride was washed with cold water, dried at 110° and weighed. As shown by the complete recovery of isatoic anhydride in the experiment with pure water the compound is practically insoluble in water, and is not hydrolyzed by it under the conditions used. The filtrate from the recovered isatoic anhydride (or the original reaction liquid if this was clear) was examined as follows.

Determination of benzoylene urea and anthranilamide. The sensible solubility of anthranilamide in water made its approximately quantitative recovery as such impracticable. Therefore in most cases it was converted to anthranilic acid by hydrolysis with aqueous sodium hydroxide and this was precipitated and determined as cupric anthranilate. The validity of this procedure is based upon the facts (a) that aqueous ammonia, under the conditions used, does not hydrolyze either isatoic anhydride or anthranilamide, so that no anthranilic acid is present from these sources; (b) that aqueous alkali converts uramidobenzoic acid to the sodium salt of benzoylene urea, which is not decomposed by alkali, so that no benzoylene urea is lost during the treatment with alkali; and (c) that in solutions which are neutral or slightly acid with acetic acid cupric acetate in excess precipitates anthranilic acid as the cupric salt (6). An experiment to test the completeness of hydrolysis and precipitation by the procedure described below showed recovery of cupric anthranilate from 0.5000 g. of anthranilamide to be 0.6190 g. or 100.4%.

Procedure. To the clear reaction liquid was added 0.5 g. of solid sodium hydroxide, and the solution was evaporated to a thick paste on a hot plate. The residue was dissolved in 50 ml. of water, and the solution was acidified with acetic acid and was chilled in an ice-bath. Any benzoylene urea present separated and was collected in a tared Gooch crucible, washed with cold water, dried at 110°, and weighed. This product was identified as ben-

zoylene urea by conversion to the dimethyl derivative (m.p. 167°) by shaking with methyl sulfate and aqueous sodium hydroxide. The filtrate from the benzoylene urea was neutralized with sodium hydroxide solution, and the solution was chilled in an ice-bath and treated with a moderate excess of cupric acetate solution (about 1 *M*). The green precipitate of cupric anthranilate was collected in a tared Gooch crucible, washed with cold water, dried at 110°, and weighed. (A brown color or a brown amorphous precipitate accompanying the cupric anthranilate appeared after about thirty minutes if the hydrolysis of anthranilamide was incomplete.)

Uramidobenzoic acid was determined either in separate experiments as follows or along with anthranilamide as outlined in the succeeding procedure. Following reaction of isatoic anhydride with ammonia the clear solution was cooled to somewhat below room temperature and was gradually acidified by addition of cold 1:1 sulfuric acid. Any separated uramidobenzoic acid was collected in a tared Gooch crucible, washed with cold water, dried at 110°, and weighed. This product was identified as uramidobenzoic acid by melting point (ca. 140°) and by its ready conversion to benzoylene urea upon treatment with hot 1:1 sulfuric acid, or by dissolving it in strong aqueous sodium hydroxide and then acidifying.

TABLE I
ACTION OF AMMONIA ON ISATOIC ANHYDRIDE
(0.01 Mol. isatoic anhydride, conc'd $\text{NH}_4\text{OH} + \text{H}_2\text{O}$ to 25 cc. Temp. 23°)

CONC'D AMMONIA MOLAR	0.0 H_2O	0.2	0.4	1.0	2.0	3.0	4.0	6.0	8.0	12.0	16.0
Molar Ratio: NH_3 to Isatoic Anhydride ..	0.0	0.5	1.0	2.5	5.0	7.5	10.0	15.0	20.0	30.0	40.0
Undissolved Isatoic Anhydride, %	100.0	79.6	20.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Anthranilamide, %	0.0	19.8	86.0	92.5	91.0	81.6	78.2	72.0	65.3	63.9	55.4
Uramidobenzoic Acid, %	0.0	0.0	0.0	0.0	9.1	15.0	23.5	28.5	30.0	38.5	39.0
Benzoylene Urea, %	0.0	0.0	0.0	0.0	10.4	17.2	20.4	30.0	34.1	34.5	41.8
Total Isatoic Anhydride Accounted for.	100.0	99.4	106.0	92.5	101.4	98.8	98.6	102.0	99.4	98.4	97.2

To determine *uramidobenzoic acid* and *anthranilamide* the clear ammoniacal reaction liquid was evaporated to dryness at or below 50°. The residue was stirred with 25 ml. of water, and any undissolved anthranilamide was collected in a tared Gooch crucible, washed sparingly with cold water, air-dried at room temperature, and weighed. The filtrate was chilled in an ice-bath and was acidified with acetic acid. After two hours in the ice-bath any uramidobenzoic acid was collected in a tared Gooch crucible and was determined. The anthranilamide in the filtrate was converted to anthranilic acid by adding 20% sodium hydroxide solution to strong alkalinity and by boiling for an hour. The solution was acidified with acetic acid and the anthranilic acid was precipitated and determined as outlined above.

Table I records results obtained by the foregoing procedures.

Effect of time. For each experiment there were used ammonia and isatoic anhydride in the molar ratio 10:1, a temperature of 25°, the general procedure given above, and reaction periods of five to forty-five minutes counted from the moment the isatoic anhydride was completely dissolved. The extent of reaction was inferred in each case from the amount of benzoylene urea isolated by the procedure described. The results were as follows:

Time, minutes	5	15	30	45
Benzoylene urea, %	21.8	20.0	21.6	20.4

It appears that reaction occurs promptly, and probably within the interval required to dissolve the isatoic anhydride.

Effect of temperature. Experiments similar to the foregoing, but with a uniform reaction period of ten minutes and with temperatures ranging from 10° to 50°, yielded these results:

Temperature °C	10	20	40	50
Benzoylene urea, %	23	22	20.6	18.5

Temperatures above room temperature appear to be without advantage; at 50° rapid change in the concentration of ammonia occurs because of volatilization.

Stability of anthranilamide toward aqueous ammonia. Anthranilamide (0.5 g.) was added to 16 *M* ammonia water (15 ml.) and the suspension was allowed to stand for twelve hours. The mixture was evaporated to dryness below 70°. The residue was treated with water and the undissolved anthranilamide was collected on a filter; the recovery was about 75%, but this value is not significant owing to the solubility of anthranilamide in water. The filtrate was adjusted to neutrality (bromocresol purple) with acetic acid and sodium hydroxide, and an excess of cupric acetate solution was added. No precipitate of cupric anthranilate appeared even after the mixture was cooled, indicating no hydrolysis of the amide by aqueous ammonia.

Reaction of aqueous ammonia and isatoic anhydride in presence of ammonium acetate. In each of the following experiments 1.63 g. (0.01 mole) of isatoic anhydride was added to aqueous ammonia previously saturated with ammonium acetate: (a) with 5 cc. of conc'd ammonia-ammonium acetate solution anthranilamide (60%) precipitated; (b, c) with 25 cc. of ammonia-ammonium acetate solution, either 4-molar or 16 molar in ammonia, no precipitate appeared, and upon acidification in the cold by addition of dilute sulfuric acid no uramidobenzoic acid separated; (d) no benzoylene urea was obtained when the reaction mixture (4-molar in ammonia) was examined for the compound by the procedure given previously; the further operations to determine anthranilamide showed presence of 90.5% of the product, a value probably somewhat low, as the solubility of cupric anthranilate is increased by presence of salts (6).

Preparation of uramidobenzoic acid or benzoylene urea from isatoic anhydride. The preparation of either of the compounds named by action of concentrated ammonia upon isatoic anhydride is easier and more rapid than by any other available method, though the yields do not exceed 40% and the process is not economical. For rapid preparation of small amounts the following procedure will serve. Isatoic anhydride is dissolved in concentrated (16 *M*) aqueous ammonia, using 15 ml. per gram of isatoic anhydride. To obtain uramidobenzoic acid the solution is chilled and then acidified slowly by addition of cold dilute sulfuric acid. To obtain benzoylene urea the reaction liquid is warmed and acidified with conc'd sulfuric acid, after which the mixture is cooled. In each case the product precipitates at once.

PHILADELPHIA 4, PA.
COLLEGEVILLE, PA.

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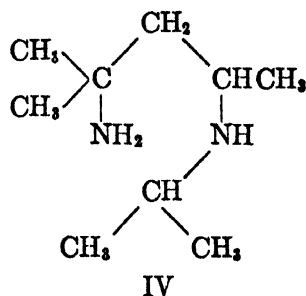
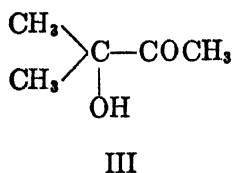
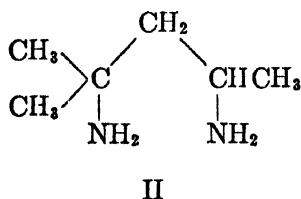
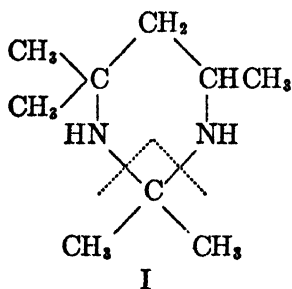
THE CONDENSATION OF 2,4-DIAMINO-4-METHYLPENTANE WITH CARBONYL COMPOUNDS

E. BERGMANN, D. HERMAN, AND E. ZIMKIN

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E. Matter (1) has recently described, as one product of interaction between acetone and ammonia, 2,2,4,6,6-pentamethyl-1,2,5,6-tetrahydropyrimidine, which could be reduced by means of sodium and alcohol to the corresponding hexahydro compound (I).¹ Its structure derives from the observation that both dilute hydrochloric acid and alcoholic sodium hydroxide solution decompose it into 2,4-diamino-4-methylpentane (II) and acetone, in the manner indicated in (I). Veer (3) had observed the same degradation, by acids, of the condensation products from 1,3-dianilinopropane and aldehydes, which he also considered as hexahydropyrimidines.

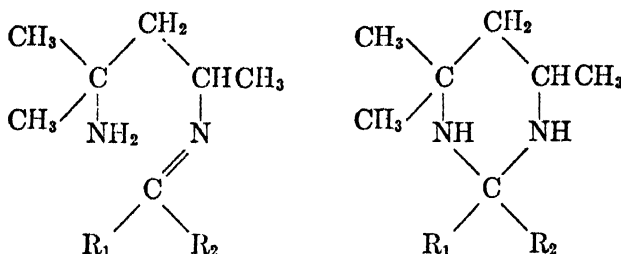
We wish to report in this connection that substances of the type (I) are obtained easily and in good yield, when a 1,3-diamine such as (II) is heated with a ketone in benzene solution in such a way that the water liberated is continuously removed in form of its azeotrope with benzene. Obviously, acetone which boils below that azeotrope (63°) cannot be condensed with (II) by this method; but 3-methyl-3-butanol-2-one (III) and cyclohexanone reacted in the desired manner. The same method can be applied advantageously to aldehydes boiling above 63°, *e.g.*, to benzaldehyde, 2-ethylhexanal or 2-ethyl-2-hexenal.



¹ Spaeth and von Szilagyi (2) have recently isolated a similar product from formiso-butyraldol and ammonia.

Acetophenone and methylisobutyl ketone did not react appreciably in boiling benzene; the desired reaction could be achieved at 150°.

Theoretically, this condensation can lead to a Schiff base as well as to a hexahydropyrimidine, *e.g.*,



The molecular refractivity permits a decision between the two formulas.² Table I shows that is is in better agreement with the heterocyclic formula. The

TABLE I
MOLECULAR REFRACTIONS

BASE	CARBONYL COMPOUND	MOL. REFRACT., FOUND	MOL. REFRACT., CALC'D FOR HETEROCYCLIC SYSTEM	SCHIFF'S BASE
2,4-Diamino-4-methyl- pentane	Methylisobutyl ketone	62.95	62.64	64.06
“ “	3-Methyl-3-butanol-2-one (IV)	59.22	59.55	59.98
“ “	Cyclohexanone	60.00	60.44	61.86
“ “	Acetophenone	67.50	68.27	69.69
“ “	Benzaldehyde	63.14	63.65	65.07
“ “	2-Ethyl-2-hexenal	70.58	71.41	72.83
Ethylenediamine	Cyclohexanone	41.27	41.94	43.36

experimental values are usually even lower than the figures calculated for the heterocyclic compounds (average deviation, -0.54). This seems to be due to the presence of the heterocyclic ring, as already emphasized by Cope and Hancock (4, 5). We are trying at present to verify this conclusion by other methods.

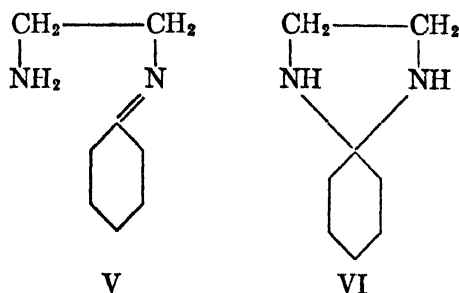
The reduction of (I) to (IV) which Matter has observed, is not in discord with the hexahydropyrimidine formula; it has been known that the rings in cyclic acetals (6) and oxazolidines³ can be opened by catalytic hydrogenation.

In Table I, the condensation product of ethylenediamine and cyclohexanone has also been included. Whilst the condensation products of this base with

² For the application of this criterion to the condensation products of α -amino alcohols and aldehydes or ketones, see Cope and Hancock (4).

³ See references (4) and (7). We have also calculated the molecular refractions of some of the more complicated oxazolidines described by Senkus: they are all heterocyclic compounds and not the isomeric Schiff's bases (No. 1, Found, 32.99; Calc'd for the oxazolidine, 33.19; for the Schiff's base, 34.64. No. 3, Found, 51.46; Calc'd, 51.63 and 53.08. No. 14, Found, 60.70; Calc'd, 60.42 and 61.87).

aldehydes have generally been assumed to be imidazolines (8), Pearson, Jones, and Cope (9) have recently condensed ethylenediamine with various ketones, without giving the products a definite structural formula. The molecular refractivity for the product from cyclohexanone is again in favor of the heterocyclic formula of a 2-(pentamethylene)imidazoline (VI). The hydrogenation of the product to N-cyclohexylethylenediamine can be interpreted equally well as that of the double bond in (V) and as ring fission in (VI).



$$\begin{array}{l}
 (\text{C} = 2.418; \text{H} = 1.100; \\
 \text{C} \begin{array}{c} \diagup \quad \diagdown \\ \text{N} \end{array} = 2.502; \quad \text{C} \begin{array}{c} \diagup \quad \diagdown \\ \text{N} = \text{C} \end{array} = 4.10^3, \quad f = 1.733, \\
 \text{C} \begin{array}{c} \diagup \quad \diagdown \\ \text{N} \quad \text{H} \end{array} = 2.322, \quad \text{O}(\text{in OH}) = 1.525).
 \end{array}$$

EXPERIMENTAL

2-Phenyl-4,6,6-trimethylhexahydropyrimidine. A mixture of 23.2 g. of 2,4-diamino-4-methylpentane (II), 21.2 g. of benzaldehyde, and 50 cc. of benzene was heated until 3.6 cc. of water had collected in the azotropic receiver. The product was distilled under 15 mm. pressure; it boiled at 155–156° and formed 33 g. of a yellowish, basic-smelling oil; d_4^{20} , 0.973; n_D^{20} , 1.5170.

Anal. Calc'd for $\text{C}_{13}\text{H}_{20}\text{N}_2$. C, 76.5; H, 9.8; N, 13.8.

Found: C, 76.3; H, 10.0, N, 14.0.

2-(α -Ethylpentyl)-4,6,6-trimethylhexahydropyrimidine. Thirty grams of the diamine (II), 33 g. of 2-ethylhexanal, 50 cc. of benzene; 5 cc. of water was liberated; b.p. 105–106°/5 mm.; yield, 53 g.

2-(α -Ethyl- Δ^{α} -pentenyl)-4,6,6-trimethylhexahydropyrimidine. Eleven and six-tenths grams of the diamine, 11.6 g. of 2-ethyl-2-hexenal, 50 cc. of benzene; 1.8 cc. of water collected in the receiver, b.p. 125°/47 mm.; a considerable resinous residue remained; yield, 5 g., d_4^{20} , 0.880; n_D^{20} , 1.4664.

Anal. Calc'd for $\text{C}_{14}\text{H}_{22}\text{N}_2$. C, 75.0; H, 12.6; N, 12.5.

Found: C, 74.7; H, 12.6, N, 12.8.

2-Phenyl-2,4,6,6-tetramethylhexahydropyrimidine. Twenty-three and two-tenths grams of the diamine (II) and 24 g. of acetophenone in 50 cc. of benzene reacted only very slowly. The two components were, therefore, heated without diluent for 4 hours at 150°. Even so, 40% of the starting materials (9.3 g. and 9.6 g., respectively) were recovered. The product, which was obtained in a yield of 26.2 g. (60% of the theory, calc'd on the total of the starting material) boiled at 155–160°/25 mm.; d_4^{20} , 0.975; n_D^{20} , 1.5191.

Anal. Calc'd for $\text{C}_{14}\text{H}_{22}\text{N}_2$. C, 77.1; H, 10.1; N, 12.8.

Found: C, 77.3; H, 10.4; N, 12.5.

2-Isobutyl-2,4,6,6-tetramethylhexahydropyrimidine. Eleven and six-tenths grams of the

diamine (II) and 10 g. of methyl isobutyl ketone were boiled for 4 hours in a short column until the expected quantity of 1.8 cc. of water had collected in the receiver. The product boiled at 125°/50 mm.; yield, almost quantitative; d_4^{20} , 0.850; n_D^{20} , 1.4513.

Anal. Calc'd for $C_{12}H_{24}N_2$: C, 72.7; H, 13.1; N, 14.1.

Found: C, 72.7; H, 13.3; N, 14.0.

2-Pentamethyleno-4,6,6-trimethylhexahydropyrimidine. Thirty-two and two-tenths grams of the diamine (II), 20 g. of cyclohexanone, and 30 cc. of benzene were distilled azeotropically until 3.6 cc. of water had collected in the receiver; b.p. 82–83°/5 mm.; yield, 31.5 g.; d_4^{20} , 0.9356; n_D^{20} , 1.4845.

Anal. Calc'd for $C_{12}H_{24}N_2$: C, 73.2; H, 12.2; N, 14.6.

Found: C, 73.3; H, 12.5; N, 14.4.

2-(α -Hydroxyisopropyl)-2,4,6-tetramethylhexahydropyrimidine. Eleven and eight-tenths grams of the diamine (II), 11.2 g. of 3-methyl-3-butanol-2-one (10) (II), and 50 cc. of benzene; 1.8 cc. of water were liberated; yellowish oil of b.p. 144°/40 mm.; yield, 17 g.; d_4^{20} , 0.931; n_D^{20} , 1.4621.

Anal. Calc'd for $C_{11}H_{24}N_2O$: C, 66.0; H, 12.0; N, 14.0.

Found: C, 65.6; H, 12.2; N, 13.9.

2-Pentamethylenoimidazolinc (VI). Twenty grams of freshly distilled ethylenediamine, 33 g. of cyclohexanone, and 50 cc. of benzene. The expected quantity of water was liberated within 15 minutes. The colorless reaction product boiled at 80–81°/8 mm.⁴; yield, 22 g., d_4^{20} , 0.988; n_D^{20} , 1.4960.

Anal. Calc'd for $C_8H_{16}N_2$: C, 68.6; H, 11.4; N, 20.0.

Found: C, 68.5; H, 11.9; N, 20.2.

REHOVOTH, PALESTINE
PHILADELPHIA, PA.

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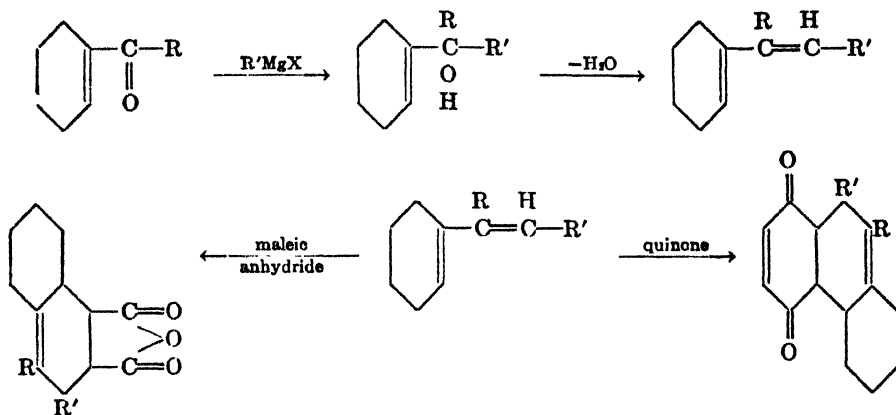
⁴ Pearson, Jones, and Cope (9) have not isolated their product, but subjected it directly to catalytic hydrogenation.

SOME $\Delta^{4,10}$ -OCTAHYDRONAPHTHALENE-1,2-DICARBOXYLIC ACID ANHYDRIDES

DOROTHY NIGHTINGALE, ERNEST C. MILBERGER, AND ARTHUR TOMISEK

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The purpose of this investigation was to prepare a series of $\Delta^{4,10}$ -octahydronaphthalene-1,2-dicarboxylic anhydrides and some decahydrophenanthraquinones by the following series of reactions



The cyclohexenyl ketones were obtained in good yields from cyclohexene and acid chlorides in the presence of either aluminum chloride or stannic chloride (1, 2, 3).

The tertiary carbinols from the reaction of the cyclohexenyl ketones with the Grignard reagents dehydrated so readily that it was difficult if not impossible to obtain them free from diolefin. The reaction of 1-cyclohexenyl isopropyl ketone and isopropylmagnesium bromide yielded mainly 1-cyclohexenylisopropyl carbinol by reduction of the ketone.

Phenylmagnesium bromide reacted with 1-cyclohexenyl methyl ketone and the ethyl ketone to form the tertiary carbinol and some 2-phenylhexahydroacetophenone and 2-phenylhexahydropropiophenone respectively by 1,4-addition to the conjugated system of the ketone.



The 2-phenylhexahydroacetophenone has recently been reported as a by-product from the aluminum chloride catalyzed reaction of 1-cyclohexenyl methyl ketone with benzene (4).

The dienes were obtained from the tertiary carbinols by distillation with iodine

or potassium acid sulfate in an atmosphere of nitrogen. They reacted readily with maleic anhydride to form the expected adducts in good yields, but solids were obtained from only two of the dienes and *p*-benzoquinone. Cook and Lawrence (5) have reported a Diels-Alder reaction of 1-vinyl-1-cyclohexene with maleic anhydride and benzoquinone. Meggy and Robinson (6) obtained 9-methyl- $\Delta^{4,10}$ -octahydronaphthalene-1,2-dicarboxylic anhydride from 1-methyl-2-vinylcyclohexene-1 and maleic anhydride.

EXPERIMENTAL

The cyclohexenyl ketones were prepared by the slow addition of 1.2 moles of aluminum chloride to 1 mole of acid chloride and 1 mole of cyclohexene in 500 cc. of carbon disulfide (3). After the complex was decomposed, washed, and dried, the reaction product was distilled under reduced pressure to separate the intermediate 2-chloro ketone from high-boiling by-products.

TABLE I
THE 2,4-DINITROPHENYLHYDRAZONES OF THE CYCLOHEXENYL KETONES

R	M P. °C.	FORMULA	CARBON, %		HYDROGEN, %	
			Calc'd	Found	Calc'd	Found
CH ₃	202-203	C ₁₄ H ₁₆ N ₄ O ₄	55.20	55.20	5.30	5.43
C ₂ H ₅	206-207	C ₁₆ H ₁₈ N ₄ O ₄	56.6	56.42	5.70	5.69
<i>n</i> -C ₃ H ₇	160-161	C ₁₈ H ₂₀ N ₄ O ₄	57.88	57.62	6.07	6.29
<i>i</i> -C ₃ H ₇	121-122	C ₁₈ H ₂₀ N ₄ O ₄	57.88	57.86	6.07	6.33
<i>n</i> -C ₄ H ₉	147-148	C ₁₇ H ₂₂ N ₄ O ₄	58.95	59.06	6.40	6.27
<i>i</i> -C ₄ H ₉	156-157	C ₁₇ H ₂₂ N ₄ O ₄	58.95	59.11	6.40	6.38
<i>n</i> -C ₅ H ₁₁	118-119	C ₁₈ H ₂₄ N ₄ O ₄	61.1	60.8	6.72	6.53

The crude 2-chloro ketones were dehydrohalogenated by distillation under reduced pressure with sodium or potassium carbonate (3). The 1-cyclohexenyl ketones so obtained were redistilled from carbonate, but this product always gave a positive Beilstein test for halogen and darkened on standing, with the formation of variable amounts of high-boiling condensation products. The cyclohexenyl ketones were further purified by heating with dimethylaniline at 180° for two hours (2, 7), to yield finally a product which was halogen-free. Ketones which had been standing for some time were redistilled just before they were used in the Grignard reaction. All the ketones studied are described in the literature with the exception of the 1-cyclohexenyl *n*-butyl and *n*-amyl ketones.

1-Cyclohexenyl n-butyl ketone; yield 59%, b.p. 133-137° (27 mm.).

Anal. Calc'd for C₁₁H₁₈O: C, 78.21; H, 11.60.

Found: C, 78.60; H, 11.32.

1-Cyclohexenyl n-amyl ketone; yield, 44%, b.p. 121-123° (18 mm.).

Anal. Calc'd for C₁₂H₂₀O: C, 79.91; H, 11.21.

Found: C, 79.95; H, 11.31.

The 2,4-dinitrophenylhydrazones of the ketones were more conveniently prepared than the semicarbazones. They are listed in Table I.

The tertiary carbinols were formed by the reaction of 0.5 mole of the cyclohexenyl ketone with 0.6 mole of a Grignard reagent containing the same alkyl radical as that in the ketone. The products were worked up in the usual manner and were distilled at as low a pressure as possible to avoid dehydration of the tertiary carbinol to the diolefin, but only two of the carbinols were obtained pure enough for analysis. All the carbinols were pale yellow, even when freshly distilled.

A sample of diethylcyclohexenyl carbinol which had stood in a cork stoppered bottle for several months became viscous and developed a dark red color. The boiling point rose from 60–61° (1 mm.) to 120–155° (5 mm.) and 20% of the material was a tarry residue.

Diethyl-1-cyclohexenyl carbinol; b.p. 60–61° (1 mm.).

Anal. Calc'd for $C_{11}H_{20}O$: C, 78.51; H, 11.92.

Found: C, 78.54; H, 12.02.

Di-n-propyl-1-cyclohexenyl carbinol; b.p. 86–88° (2 mm.).

Anal. Calc'd for $C_{13}H_{24}O$: C, 79.53; H, 12.32.

Found: C, 79.02; H, 12.18.

Isopropyl-1-cyclohexenyl carbinol. The product from the reaction of 1-cyclohexenyl isopropyl ketone and 0.6 mole of isopropylmagnesium bromide distilled at 74–120° (4 mm.). Careful fractionation of this material yielded 36 g. of isopropyl-1-cyclohexenyl carbinol, b.p. 115–118° (18 mm.); n_D^{20} 1.4645.

Anal. Calc'd for $C_{10}H_{18}O$: C, 77.85; H, 11.77.

Found: C, 77.93; H, 12.07.

Reaction of 1-cyclohexenyl methyl ketone with phenylmagnesium bromide. The ketone (0.52 mole) in 100 cc. of dry ether was added to the Grignard reagent from 0.78 mole of bromobenzene in 200 cc. of ether. The reaction product was separated first into three

TABLE II
THE DIENES

	B.P., °C./MM	n_D , t	FORMULA	CARBON, %		HYDROGEN, %	
				Calc'd	Found	Calc'd	Found
2-(1-Cyclohexenyl)-2-propene.	66–68/20	26° 1.4978	C_9H_{14}	88.45	88.13	11.55	11.36
3-(1-Cyclohexenyl)-2-butene	55–56/4	28° 1.4863	$C_{11}H_{18}$	87.86	87.95	12.07	12.27
3-(1-Cyclohexenyl)-2-heptene	70–71/3	27° 1.4892	$C_{13}H_{22}$	87.56	87.70	12.44	12.34
2, 6 - Dimethyl - 4 - (1 - cyclohexenyl) - 3-heptene . . .	76–77/1	26° 1.4708	$C_{15}H_{26}$	87.28	86.95	12.74	12.94

ractions: (I) 14 g. b.p. 64–80° (4 mm.); (II) 43 g. b.p. 80–85° (4 mm.); (III) 17 g. residue. Careful fractionation of (I) and (II) and molecular distillation of the residue yielded an impure tertiary carbinol and a white solid distilling above 105° (5 mm.). Crystallization of the solid from alcohol yielded 8 g. of 2-phenylhexahydroacetophenone m.p. 79–80° (4).

Anal. Calc'd for $C_{14}H_{18}O$: C, 83.13; H, 8.97.

Found: C, 82.99; H, 9.13.

The 2,4-dinitrophenylhydrazone of this ketone melted at 140–141°, the recorded melting point (4).

1-Cyclohexenyl ethyl ketone reacted similarly to yield impure tertiary carbinol and 6–8% of 2-phenylhexahydropropiophenone, a viscous oil which would not solidify, and which could not be purified. The oil reacted with 2,4-dinitrophenylhydrazine to form a 2,4-dinitrophenylhydrazone of 2-phenylhexahydropropiophenone which crystallized from alcohol in pale orange plates, m.p. 132–133°.

Anal. Calc'd for $C_{21}H_{24}N_4O_4$: C, 63.60; H, 6.10.

Found: C, 63.75; H, 6.26.

Analyses of the tertiary carbinol fractions indicated the presence of diolefin.

The dienes. The dienes were obtained from the tertiary carbinols either by heating them with potassium bisulfate or with iodine in an atmosphere of nitrogen just prior to distillation under diminished pressure. They were dried briefly and used directly in the Diels-Alder reactions. The samples for analyses and physical constants listed in Table II were dried over sodium and were carefully fractionated in an atmosphere of nitrogen. They were analyzed immediately after distillation.

The Diels-Alder reactions. The dienes were added to maleic anhydride dissolved in xylene (5). After warming on a water-bath, the solution was allowed to stand for several days. The solvent was removed under diminished pressure, leaving a sticky solid which was purified by digestion with water and finally by crystallization from petroleum ether. The acid anhydrides were obtained as fine colorless needles. Yields ranged from 21% to 41%.

The condensations of the dienes with *p*-benzoquinone were carried out in methyl alcohol solution. The reactants were mixed, allowed to stand overnight, then refluxed two hours. The solvent was removed on a water-bath, leaving a red oil which solidified on standing in the ice-chest. The solid was crystallized from methyl alcohol to yield yellow needles. Pure diketones were obtained from only two of the dienes.

These condensation products are listed in Table III.

TABLE III
THE $\Delta^{4,10}$ -OCTAHYDRONAPHTHALENE-1,2-DICARBOXYLIC ANHYDRIDES

R	R'	M.P., °C.	FORMULA	CARBON, %		HYDROGEN, %	
				Calc'd	Found	Calc'd	Found
CH ₃	H	76.2	C ₁₃ H ₁₆ O ₃	70.88	70.68	7.32	7.82
C ₂ H ₅	CH ₃	92.8	C ₁₅ H ₂₀ O ₃	72.53	72.22	8.12	8.49
<i>n</i> -C ₃ H ₇	C ₂ H ₅	105.8	C ₁₇ H ₂₄ O ₃	73.88	73.58	8.75	8.75
<i>i</i> -C ₄ H ₉	<i>i</i> -C ₃ H ₇	145	C ₁₉ H ₂₈ O ₃	74.95	74.76	9.27	9.23

THE 5,8-DIKETO- $\Delta^{6,7}$, $\Delta^{10,10a}$ -DECAHYDROPHENANTHRENES							
CH ₃	H	102	C ₁₅ H ₁₈ O ₂	78.23	78.01	7.88	7.88
<i>n</i> -C ₃ H ₇	C ₂ H ₅	84	C ₁₉ H ₂₆ O ₂	79.68	79.59	9.15	9.23

SUMMARY

A convenient method has been developed for the preparation of substituted 1-vinyl-1-cyclohexenes. These dienes react readily with maleic anhydride to form $\Delta^{4,10}$ -octahydronaphthalene-1,2-dicarboxylic anhydrides.

2-Phenylhexahydroacetophenone and 2-phenylhexahydropropiophenone were isolated from the reaction of 1-cyclohexenyl methyl and ethyl ketones respectively with phenylmagnesium bromide.

COLUMBIA, MISSOURI

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THE ISOMERS OF 4-PHENYL- AND 4-CYCLOHEXYL-CYCLO- HEXANOL

HERBERT E. UNGNADE

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The preparation and determination of configuration of the geometric isomers has been carried out only for a few simple 4-substituted alkyl cyclohexanols (1, 2, 3, 4). All of these are liquids. The similarity of the physical properties of the liquid isomers makes it difficult to ascertain the purity of a given preparation or to estimate the composition of mixtures of isomers. Since a pure liquid compound can be obtained with certainty only by regeneration from solid derivatives, unstable forms which might be present are lost. The present study was undertaken with the aim of preparing solid cyclohexanols which could be studied singly or in mixtures, before and after regeneration from derivatives.

The starting materials for this investigation, 4-phenyl- and 4-cyclohexylcyclohexanone, were obtained by oxidation of crude cyclohexanol mixtures and purified by regeneration from their oximes.

A mixture of 4-cyclohexylcyclohexanols is the main product when *p*-hydroxydiphenyl is hydrogenated at 210° (200 atm.) over Raney nickel catalyst. If the reduction is carried out at 140–170° in the presence of a small amount of the sodium salt of *p*-hydroxydiphenyl, the formation of the 4-phenylcyclohexanols is favored (5, 6).

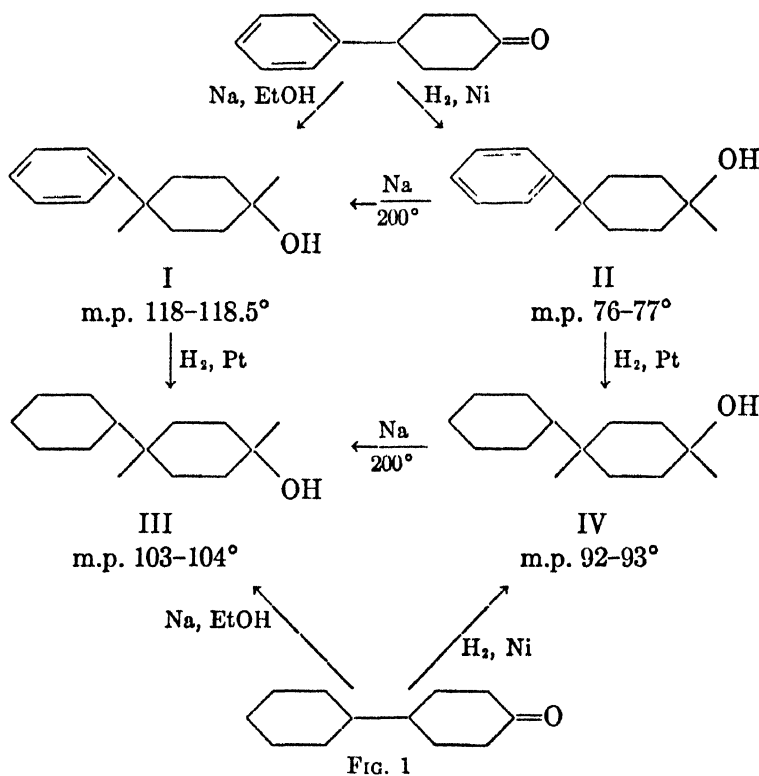
Reduction of 4-phenylcyclohexanone with sodium and alcohol yields a nearly pure alcohol (I) melting at 117.2–118.5° which is identical with the substance isolated in this laboratory some time ago (5) and with the product of Musser and Adkins (7). The hitherto unknown isomer (II), m.p. 76–77°, is formed in good yield by the hydrogenation of this ketone with Raney nickel catalyst at room temperature under a slight pressure of hydrogen. The hydrogenation of this ketone with platinum catalyst in acetic acid solution is particularly unsatisfactory because of side reactions which affect the benzene ring and the hydroxyl group.

The product obtained by reducing 4-cyclohexylcyclohexanone with sodium and alcohol melts at 103–104° (III). It is identical with the "*cis*"-alcohol of Schrauth and Görig (10) and others (11) and with the cyclohexylcyclohexanol of Musser and Adkins (7, 5). The isomeric cyclohexanol (IV) cannot be separated directly from the mixture which results when the ketone is reduced with Raney nickel or platinum catalyst at room temperature. It is obtained by fractional crystallization of the dinitrobenzoates and hydrolysis of the pure ester, and melts at 92–93°. The compound described in the literature melting at 83–84° (10, 11) must be regarded as a mixture of isomers.

Since an absolute method for determining configuration is not available for 4-alkyl- and 4-aryl-cyclohexanols, the structures of the isomers in this series are

assigned on the basis of methods of formation, physical properties, reaction rates, and isomerization studies.

The phenylcyclohexanol (I), m.p. 118–118.5° (after purification) is assigned the *trans*-configuration because of its method of formation (8) and because it is obtained from the *cis*-isomer (II), m.p. 76–77° by inversion with sodium at 200° (9). The *trans*-alcohol (I) shows a larger molecular weight in ethylene bromide than the isomer (II) (Fig. 4) which is in agreement with the generalization established by Hückel (17). The concentration dependency, on the other hand, appears to be reversed, since the molecular weight of the *cis*-alcohol (II) in-



creases more rapidly with concentration than that of the alcohol (I). Abnormalities in the concentration dependency of the molecular weights of other cyclohexanols have been observed by Hückel and have been ascribed to the solvent (18). The small solubilities of the compounds unfortunately prevented the determination of the molecular weights in other solvents.

The *trans*-configuration of the 4-cyclohexylcyclohexanol (III), m.p. 103–104°, is based upon its preparation from 4-cyclohexylcyclohexanone by reduction with sodium and alcohol (8). It is formed in good yield also from the *cis*-isomer (IV), m.p. 92–93°, by inversion with sodium (9) and its 3,5-dinitrobenzoate is saponified more easily than that of the *cis*-alcohol (IV) (12). The configuration of the *cis*-alcohol (IV) follows from its formation by catalytic hydrogenation of the

corresponding ketone with platinum in acetic acid solution. The cryoscopic behavior of the 4-cyclohexylcyclohexanols parallels that of the 4-phenylcyclohexanols.

The pure phenylcyclohexanols have been converted to the corresponding cyclohexylcyclohexanols by hydrogenation with Adams' catalyst in acetic acid solution. The relationship of the compounds is given in Figure 1. The *cis*-alcohol (II) is hydrogenated nearly twice as fast as the isomer (I) (Fig. 2), the reaction continues after the aromatic ring is saturated, and the hydroxyl group is eliminated quantitatively to give dicyclohexyl. The rate of hydrogenolysis is greater for the *cis*-alcohol (IV) than for the *trans*-isomer (III) (Fig. 3). A similar relationship has been observed by Chiurdoglu in the hydrogenolysis of

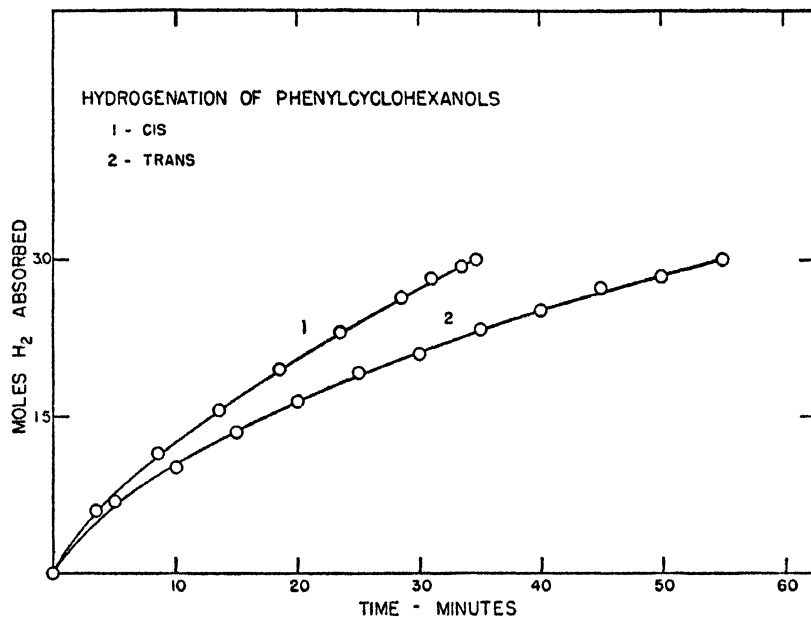


Fig. 2

the 1,2-dialkylcyclopentanols (13) and the 1,2- 1,3- and 1,4-dialkylcyclohexanols (14). The alcohol with *cis*-configuration of hydroxyl and the second alkyl group is reduced more rapidly than its isomer.

The cyclohexanol mixtures which are obtained from the reduction of 4-phenyl- and 4-cyclohexyl-cyclohexanone have been found to correspond to mixtures of pure *cis*- and *trans*-isomers by comparison with the melting point-composition diagrams. It is particularly interesting to note that mixtures resulting from the reduction of the ketones with Raney nickel at room temperature correspond to eutectic points in the melting point diagrams.

Chromatographic adsorption on alumina has been found useful for the purification of both pairs of isomers although a complete separation by this method has succeeded only with the phenylcyclohexanols. The *trans*-alcohol in each case is more strongly adsorbed than the *cis*-isomer. This relationship appears to

apply to 4-substituted cyclohexanols generally (15, 16) and is suggested as a method to determine configuration.

EXPERIMENTAL

All temperatures uncorrected.

Analyses by the students in my course in organic quantitative semimicro analysis.

Hydrogenation of *p*-hydroxydiphenyl. *p*-Hydroxydiphenyl (100 g.) was dissolved in a solution of sodium methoxide containing 0.06 g. of sodium in 100 cc. of absolute methanol. Raney nickel (6 g.) was added to the resulting solution and the mixture was immediately hydrogenated under an initial pressure of 2700 lbs. The temperature was raised rapidly to 140° and maintained until the absorption of hydrogen ceased or else it was raised to 170° and the reaction stopped at this point.

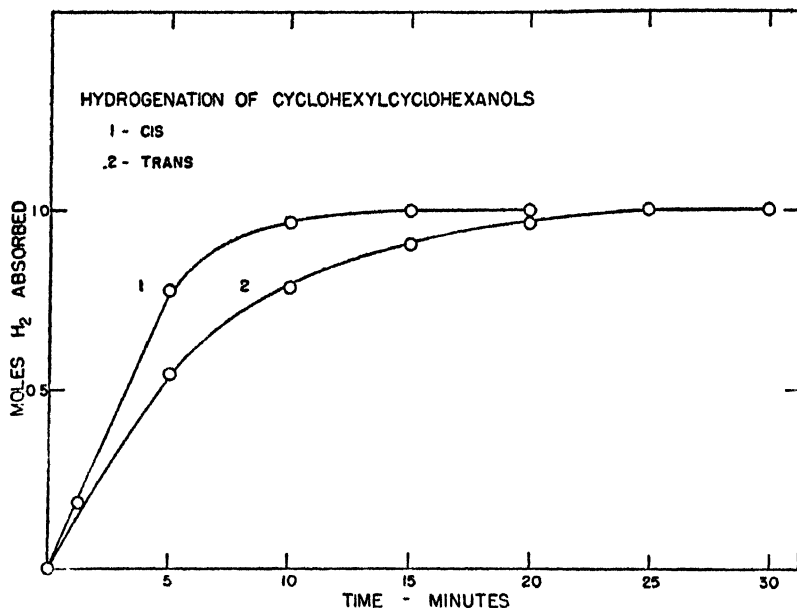


Fig. 3

The methanol solution was filtered from the catalyst and distilled to remove the solvent. The remaining glassy material was dissolved in benzene and was extracted with 5% aqueous potassium hydroxide solution to remove phenolic material. The benzene solution was washed with water, dried by removing the benzene-water azeotrope, and distilled. The residual oil (98 g.) consisted of a mixture of 4-phenyl- and 4-cyclohexyl-cyclohexanols. It was used directly for the preparation of 4-phenylcyclohexanone.

The alkali-soluble portion upon acidification gave nearly pure (approximately 95%) *p*-cyclohexylphenol melting at 127–129°. Crystallization from benzene raised the melting point to 129–130°; mixed melting point with authentic material 129–130°.

For the preparation of the cyclohexylcyclohexanols, the hydrogenation of *p*-hydroxydiphenyl (100 g.) was carried out by shaking the solution in 100 cc. of methanol with 12 g. of Raney nickel at 210° under a starting pressure of 3000 lbs. until the absorption of hydrogen ceased.

4-Phenylcyclohexanone. Concentrated sulfuric acid (66 g.) was added to 200 cc. of water contained in a 2-liter three-necked flask equipped with a thermometer and efficient stirrer.

The mixture was cooled to 20°. The crude mixture of 4-phenyl- and 4-cyclohexyl-cyclohexanols (182 g.) was added to this solution with stirring. To the resultant suspension was added 150 cc. of glacial acetic acid with stirring and the mixture was packed in ice. The addition of the oxidizing solution was started immediately, dropwise, with stirring at such a rate that the temperature did not rise.

The oxidizing solution consisted of 66 g. of concentrated sulfuric acid, 100 g. of sodium dichromate, and 200 cc. of water, and was cooled to 20° before the addition.

After completed addition, another 50-cc. portion of acetic acid was added, the ice-bath was removed, and the reaction mixture was immersed in a cold water-bath. The temperature of the mixture was raised to 60° during 2.5 hours, then it was allowed to stand overnight. The mixture was extracted with ether and the extract washed with water, 10% aqueous sodium hydroxide solution, and again with water. The ether layer was stirred vigorously with 1500 cc. of saturated aqueous sodium bisulfite solution for two hours. The addition compound was washed twice with 95% ethyl alcohol and twice with ether and air dried. The dry powder was stirred with 1000 cc. of cold 10% aqueous sodium hydroxide solution. The oily ketone was extracted with benzene. The extracts were washed with water, filtered, and distilled from a water-bath. The residual ketone (162 g.) was crystallized from petroleum ether (28–38°). The yield of 4-phenylcyclohexanone was 73 g., m.p. 77–78°.

4-Phenylcyclohexanone oxime. A mixture of 10 g. of ketone, 30 cc. of methanol, 10 g. of hydroxylamine hydrochloride in 15 cc. of water, and 10 g. of sodium acetate in 15 cc. of water gave 10.5 g. of dry oxime which melted at 110–111° after crystallization from ligroin (60–100°). Repeated crystallizations from the same solvent gave the constant melting point 112–113°.

Anal. Calc'd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40; M.W., 189.

Found: C, 75.99, 76.07; H, 8.10, 7.95; N, 7.40, 7.38, 7.34; M.W., 185 (Rast).

The oxime (5 g.) was hydrolyzed by heating with 100 cc. of 10% aqueous sulfuric acid. The ketone was isolated by steam distillation. After crystallization from ligroin (60–70°) the product showed the melting point 78–79° and the freezing point 77.7° (from the cooling curve).

Reconversion of this ketone to the oxime gave an excellent yield of a product melting at 112–113°.

The semicarbazone of the pure ketone (0.5 g.) prepared with 10 cc. of methanol, 0.7 g. of semicarbazide hydrochloride in 1.5 cc. of water, and 1.0 g. of sodium acetate in 1.5 cc. of water melted at 211–212° (dec.). Crystallization from methanol raised the melting point to 211.5–212.5° (dec.). The melting point of v. Braun and Weissbach (229° dec.) (19) was obtained for this material by using the Dennis bar method.

trans-4-Phenylcyclohexanol (I). Pure 4-phenylcyclohexanone (20 g.) was reduced with sodium (20 g.) and 200 cc. of absolute ethyl alcohol. The mixture was refluxed and, while still warm, was decomposed with 800 cc. of water. The product was taken up in benzene, washed with water, and distilled. The solid residue (20 g.) on crystallization from ligroin (60–70°) gave 13.0 g. of the alcohol melting at 116–117.5°. Another crystallization from ligroin (85–100°) raised the melting point to 117.2–118.5° (yield 12.2 g.). The mixed melting point of this material with the 4-phenylcyclohexanol (m.p. 116–117°) previously described (5) was 116–117.5°.

Phenylurethan. The phenylurethan prepared from 2.2 g.¹ of the above alcohol by refluxing with 1.8 cc. of phenylisocyanate in 50 cc. of ligroin (85–100°), melted at 138–139.5°, yield 3.0 g. Several crystallizations from the same solvent gave the constant melting point 140–140.5°.

Anal. Calc'd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.16; N, 4.74; M.W. 295.3.

Found: C, 77.28, 77.33; H, 7.32, 7.27; N, 4.62; M.W. 275 (Rast).

The purified phenylurethan (3.93 g.) was ammonolyzed with 50 cc. of concentrated ammonia by heating under pressure at 160° for one hour. The reaction mixture was worked up as described previously (4). The product (2.41 g.), m.p. 109–112°, contained unchanged urethan which could not be separated by crystallization. Adsorption of the mixture on

alumina (General Chemical Co., ignited powder, reagent) from ligroin (85–100°) solution and elution with the same solvent yielded 0.65 g. of pure phenylurethan, m.p. 140–140.5°. Subsequent elution with benzene gave 1.0 g. of pure *trans*-4-phenylcyclohexanol melting at 118–118.5° (from ligroin, 60–70°). Its mixture with the starting material melted at 117.2–118.5°.

Benzoate. Benzoylation of the *trans*-alcohol with benzoyl chloride in pyridine in the cold gave a benzoate melting at 104.5–105.5° (from ligroin, 60–70°).

Anal. Calc'd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19.

Found: C, 81.01, 81.23; H, 7.41, 7.64.

***p*-Toluenesulfonate.** The *p*-toluenesulfonate, prepared in the usual way, was stable toward boiling methanol. It melted at 98.2–98.7° after several crystallizations from methanol. Hydrolysis of the *p*-toluenesulfonate gave only the olefin.

Anal. Calc'd for $C_{19}H_{22}O_3S$: C, 69.07; H, 6.71.

Found: C, 69.13; H, 6.71.

***cis*-4-Phenylcyclohexanol (II).** 4-Phenylcyclohexanone (1.74 g., 0.01 mole) dissolved in 30 cc. of methanol was hydrogenated with 3 g. of Raney nickel under a pressure of 30 mm. of hydrogen. The absorption of hydrogen stopped when the theoretical amount was taken up. The mixture was filtered and the filtrate freed from solvent. The residue (1.61 g.) solidified on cooling and melted at 59–61°. Crystallization or adsorption on alumina from ligroin (85–100°) solution gave small amounts of the *trans*-alcohol melting at 117.5–118.2° but failed to separate the bulk of the material. A complete separation was effected by adsorbing the mixture (1.3 g.) on alumina from ligroin (30–60) solution. Elution with the same solvent yielded 0.50 g. of *cis*-isomer melting at 76–77°. The mixed melting point of this substance with the ketone (m.p. 77–78°) was 49–56° and the mixed melting point with the *trans*-alcohol (m.p. 118–118.5°) was 62–92°.

Anal. Calc'd for $C_{12}H_{16}O$: C, 81.78; H, 9.15.

Found: C, 81.77, 81.69, 81.81; H, 9.07, 9.01, 9.07.

Further elution of the column with benzene gave 0.16 g. of crystalline material melting at 62–66° which was a mixture of the isomers. The subsequent methanol eluate contained 0.13 g. of the *trans*-isomer melting at 118–118.5° which did not depress the melting point of an authentic specimen.

Phenylurethan. The crystalline phenylurethan of the *cis*-alcohol (II) melted at 140.5–141°. The mixture with the isomeric urethan (m.p. 140–140.5°) melted at 115–124°.

Anal. Calc'd for $C_{15}H_{21}NO_2$: C, 77.26; H, 7.16; N, 4.74; M.W., 295.3.

Found: C, 77.36; H, 7.34; N, 4.61, 4.78; M.W. 296 (Rast).

The alcohol (II) was recovered unchanged after standing for ten days at room temperature with 3,5-dinitrobenzoyl chloride in pyridine.

Inversion of *cis*-4-phenylcyclohexanol (II). The pure *cis*-alcohol (II) (0.5 g.) was heated with sodium at 200° for 3 hours as described previously (4). The reaction product (0.42 g.) after crystallization from ligroin (60–70°) melted at 105.5–116°, yield 0.30 g. Its mixture with the pure *trans*-isomer melted at 114–118°.

4-Cyclohexylcyclohexanone. The crude mixture of 4-cyclohexylcyclohexanol isomers (182 g.) (either from the hydrogenation of 4-hydroxydiphenyl or the Eastman technical grade) when oxidized with chromic acid as described for 4-phenylcyclohexanone yielded 160 g. of crude ketone. Without further purification this material, dissolved in 300 cc. of methanol, was converted to the oxime by treating with a solution of 120 g. of hydroxylamine hydrochloride in 180 cc. of water and a solution of 120 g. of sodium acetate in 180 cc. of water. The mixture was heated and the oxime was isolated in the usual way. The crude oxime melting at 72–89° weighed 179.6 g. Digestion with petroleum ether (28–38°) and crystallization from the same solvent gave 102.7 g. of pure oxime melting at 100–101°. Repeated crystallization gave the constant melting point 101–102°.

Anal. Calc'd for $C_{12}H_{21}NO$: C, 73.78; H, 10.84; N, 7.16; M.W., 195.

Found: C, 73.79, 73.62; H, 10.85, 10.97; N, 6.99, 7.20; M.W., 198 (Rast).

Hydrolysis of the oxime (102.7 g., m.p. 100–101°) with a solution of 100 cc. of concentrated

sulfuric acid in 900 cc. of water at 90° for 1.5 hour gave 81.6 g. of ketone boiling at 70–72° (0.1 mm.). This material had the freezing point 29.2° (from the cooling curve). Reconversion to the oxime gave 95.4% of pure material melting at 101–102°.

The capillary melting point of the semicarbazone was 205–206° (dec.) (Schrauth and Görig give 204–205°) (10), whereas the Dennis bar method gave a value of 210°; v. Braun reports 216° (20).

trans-4-Cyclohexylcyclohexanol (III). Reduction of the pure ketone (20 g.) with sodium (20 g.) in 200 cc. of absolute alcohol gave 17.2 g. of crystalline alcohol which melted at 103–104° after several crystallizations from 60–70° ligroin.

Phenylurethan. The phenylurethan prepared from this alcohol melted at 156–156.8° (from methanol) and is undoubtedly identical with the substance described by v. Braun *et al.* (20).

Anal. Calc'd for $C_{15}H_{27}NO_2$: C, 75.71; H, 9.03.

Found: C, 75.85, 75.80; H, 9.14, 9.09.

3,5-Dinitrobenzoate. Esterification of the alcohol (III) (0.54 g.) with 3,5-dinitrobenzoyl chloride (0.69 g.) in 8 cc. of pyridine at room temperature yielded 0.95 g. of ester melting at 138–139° after standing for four days. One crystallization from 85–100° ligroin raised the melting point to 149.5–150° which was unchanged by further crystallization.

Anal. Calc'd for $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.42.

Found: C, 60.75; H, 6.35.

Hydrolysis of the pure dinitrobenzoate (0.41 g.) with a solution of 0.4 g. of sodium hydroxide in 40 cc. of methanol and 40 cc. of water gave 0.10 g. of solid, m.p. 102–103.5°, which after one crystallization from 85–100° ligroin melted at 103.5–104°.

cis-4-Cyclohexylcyclohexanol (IV). 4-Cyclohexylcyclohexanone (5.39 g.) dissolved in 30 cc. of methanol was reduced with 3 g. of Raney nickel at 28° under a pressure of 30 mm. of hydrogen. The reduction stopped after absorbing 1 mole of hydrogen. The product melted at 80.5–81.5°, yield 5.10 g. Repeated fractional crystallizations and adsorption of this material or the substance obtained by reducing the ketone with platinum in acetic acid gave some *trans*-alcohol, m.p. 100–102°, and a mixture of isomers which melted at 83–87° and could not be further separated by crystallization or adsorption. It is presumably this material which Schrauth and Görig described as their "*trans*"-isomer (10). The fractions melting at 83–87° (3.7 g.) were esterified with 3,5-dinitrobenzoyl chloride in 50 cc. of pyridine at room temperature. The 3,5-dinitrobenzoates were obtained in 92% yield after three days, m.p. 128–147°. The dinitrobenzoates of other fractions were also prepared and all of them were fractionally crystallized. The highest melting fractions were combined and further crystallized until a homogeneous product was obtained which melted at 161–162° and depressed the melting point of the isomeric benzoate.

Anal. Calc'd for $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.42.

Found: C, 60.36; H, 6.15.

Hydrolysis of the dinitrobenzoate took place only very slowly with the dilute alkaline solution used for the isomeric benzoate. The pure *cis*-alcohol was obtained by hydrolysis of the dinitrobenzoate (4.88 g.) with 8.0 g. of potassium hydroxide in a solution of 40 cc. of water and 80 cc. of methanol. The product melting at 92–93° weighed 2.36 g. Its melting point was unchanged by crystallization from 28–38° petroleum ether. The mixture with the *trans*-isomer, m.p. 103–104° melted at 81.5–93.5°.

Anal. Calc'd for $C_{12}H_{18}O$: C, 81.78; H, 9.15.

Found: C, 81.73; H, 9.21.

Phenylurethan. The phenylurethan of the alcohol (IV) was crystallized from 60–70° ligroin. It showed two melting points, at 107–108° and 111–112°. The lower-melting form was converted to the higher-melting form by slow heating above its melting point. The reported phenylurethan melting at 103° (20) was probably impure.

Anal. Calc'd for $C_{15}H_{27}NO_2$: C, 75.71; H, 9.03.

Found: C, 75.93; H, 9.16.

Rearrangement of cis-4-cyclohexylcyclohexanol. Heating of the pure *cis*-alcohol (IV)

(0.3 g.) with 0.039 g. of sodium at 200–210° brought about the expected inversion to the *trans*-isomer. The crude product (0.17 g.) after crystallization from 60–70° ligroin melted at 102.5–104° and did not depress the melting point of an authentic sample.

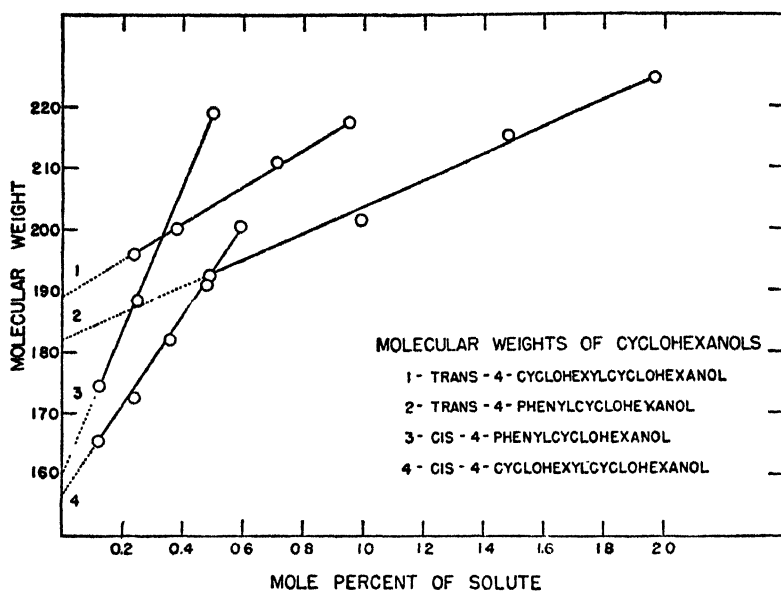


FIG. 4

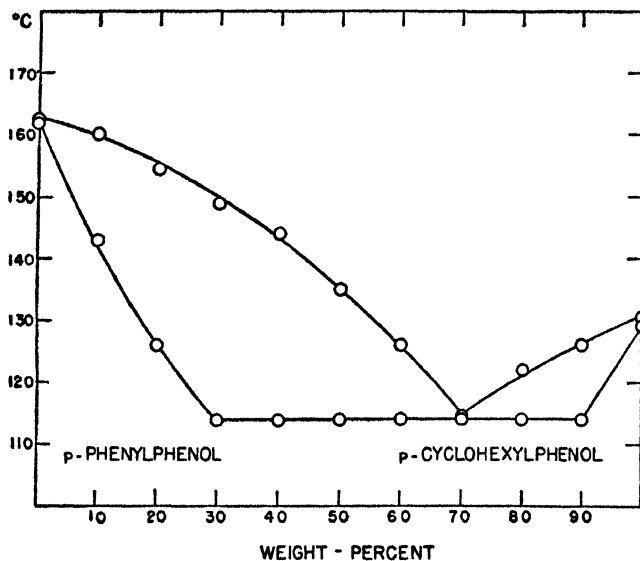


FIG. 5

Catalytic hydrogenation of the pure cyclohexanols. Both *cis*- and *trans*-4-phenylcyclohexanol (0.1 g. each) were hydrogenated at 26° under carefully controlled conditions in 20 cc. of acetic acid solution with 0.1 g. of Adams' catalyst (Fig. 2). The reaction was interrupted after absorption of the calculated amount of hydrogen and the products were

isolated by dilution with water and extraction with benzene. The single product in each case was crystallized from ligroin. Neither *cis*- nor *trans*-4-cyclohexylcyclohexanol, m.p. 90.5–92° and 101–103°, depressed the melting point of an authentic specimen.

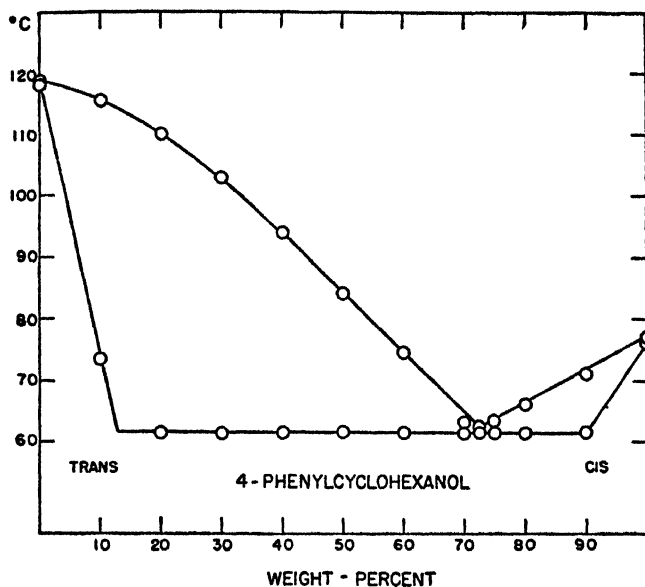


FIG. 6

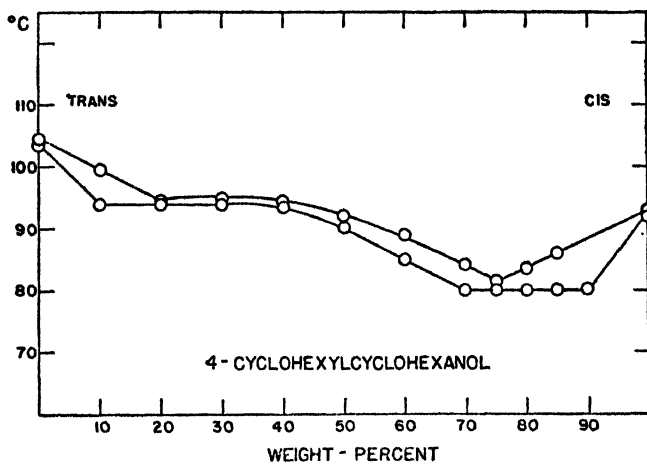


FIG. 7

The hydrogenation of *cis*- and *trans*-4-cyclohexylcyclohexanol (0.05 g. each) at 28° with platinum catalyst (0.1 g.) in 20 cc. of acetic acid (Fig. 3) stopped after absorption of one mole of hydrogen. The oily dicyclohexyl which was formed was not further investigated.

Molecular weights of the cyclohexanols. The molecular weights of the pure cyclohexanols were determined cryoscopically in pure ethylene bromide as a function of concentration (Fig. 4). Supercooling was held to 0.2° by seeding, and errors were eliminated by check runs with freshly prepared solutions.

Melting point diagrams. The melting point diagrams for mixtures of *p*-phenylphenol and *p*-cyclohexylphenol (Fig. 5) and the two pairs of *cis*, *trans*-isomers were obtained ac-

ording to the procedure of Rheinboldt (21). Mixtures of *cis*- and *trans*-4-phenylcyclohexanol (Fig. 6) and the two phenols (Fig. 5) each gave a system with a single eutectic point. In the case of the cyclohexylcyclohexanol isomers, however, two eutectic points were obtained. The diagram (Fig. 7) is indicative of compound formation and some miscibility.

ACKNOWLEDGMENTS

The author wishes to thank the Research Council of the University of Missouri for a grant which made this work possible and the University of Colorado for the privilege of using its chemical laboratories during the summer of 1947.

SUMMARY

The pure *cis*- and *trans*-isomers of 4-phenyl- and 4-cyclohexyl-cyclohexanol have been prepared and characterized by derivatives. The configurations of the compounds have been established independently and by interconversion.

The hydrogenation of 4-phenylcyclohexanone and 4-cyclohexylcyclohexanone with Raney nickel at room temperature yields mixtures of isomers which correspond to eutectic points in the melting point-composition diagrams. *cis*-4-phenylcyclohexanol is more difficult to esterify than *cis*-4-cyclohexylcyclohexanol.

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THE CHLORINATION OF 1,5-DIHYDROXYNAPHTHALENE

R. H. THOMSON

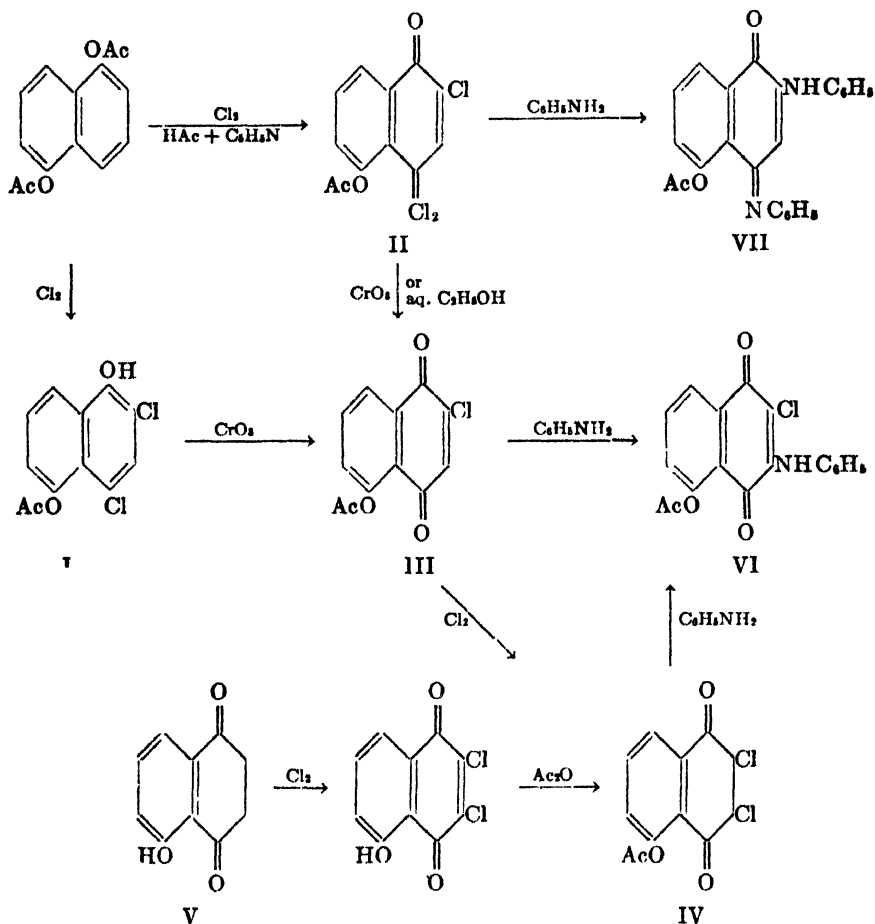
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According to Willstätter and Schuler (1) who first studied the subject, chlorination of 1,5-dihydroxynaphthalene yields the diacetate of 4,8-dichloro-1,5-dihydroxynaphthalene but no evidence was submitted in support of this structure. Subsequently, Wheeler and Mattox (2) chlorinated 1,5-diacetoxynaphthalene in carbon tetrachloride, obtaining a dichloro compound at room temperature, and a trichloro derivative at 80°, one acetyl group being hydrolyzed in each case. These products were stated to be 4,8-dichloro-5-acetoxy-1-naphthol and 4,4,8-trichloro-5-acetoxy-1-hydroxy-3,4-dihydronaphthalene respectively, since oxidation of the dichloro compound with chromic acid yielded a monochloro-5-acetoxy-1,4-naphthoquinone with elimination of one atom of chlorine, and the same quinone was obtained by oxidation of the trichloro compound with elimination of two atoms of chlorine. This however, did not afford a complete proof of the structures put forward: the location of a chlorine atom in the 8-position was not established, and also, the physical properties of the products obtained by acetylation and by hydrolysis of the dichloro compound differed somewhat from those described by Willstätter and Schuler (1). Since it has now been shown (3) that bromination of 1,5-dihydroxynaphthalene and 1,5-diacetoxynaphthalene in cold glacial acetic acid yields, 2,6-dibromo-1,5-dihydroxynaphthalene and 2,4-dibromo-5-acetoxy-1-naphthol respectively, there is reason to doubt the constitutions assigned to the chloro compounds cited above, and the present study was designed to ascertain their true structures.

Attempts to chlorinate 1,5-dihydroxynaphthalene according to the method of Willstätter and Schuler (1) were unsuccessful. In all cases small amounts of dark colored substances were obtained from which no definite compound could be isolated. This was disappointing, as confirmation of the unusual simultaneous chlorination and acetylation reported, was most desirable. The use of other chlorinating agents was likewise without result. In view of this, it is perhaps significant that Wheeler and Mattox (2) found it preferable to chlorinate the diacetate. Repetition of the work of the latter authors substantially confirmed their experimental results, although it was found more convenient to chlorinate in glacial acetic acid. Oxidation of the dichloro-5-acetoxy-1-naphthol (I) obtained, with chromic acid, yielded a monochloro-5-acetoxy-1,4-naphthoquinone (III), a chlorine atom in the para position to the hydroxyl group being removed. Further chlorination of this quinone afforded the dichloro derivative described by Wheeler and Mattox (2) as 2,8-dichloro-5-acetoxy-1,4-naphthoquinone. However, it has now been found that this compound is identical with 2,3-dichloro-5-acetoxy-1,4-naphthoquinone (IV) which was first prepared by Wheeler and Scott (4) by chlorination of juglone (V) followed by acetylation.¹ Furthermore, the anilino derivative (VI) of the monochloroquinone (III) is identical

¹ For further proof of the structure of this compound see the following paper

with that obtained from the dichloroquinone (IV) by replacement of one atom of chlorine. The structure assigned to (IV) by Wheeler and Mattox is therefore incorrect, and this compound is actually 2,3-dichloro-5-acetoxy-1,4-naphthoquinone. It is thus clear that the chlorine atom in (III) must lie in the quinone ring. Hence both chlorine atoms in (I) must have entered the ring containing the hydroxyl group, and therefore occupy the ortho and para positions. In support of this the dichloro-1,5-dihydroxynaphthalene obtained by hydrolysis of (I) gives an immediate blue-violet coloration with 2,6-dichlorobenzoquinone-4-



chloroimide, indicating that the para position to one of the hydroxyl groups is unsubstituted (5). Chlorination of 1,5-diacetoxynaphthalene at room temperature thus yields 2,4-dichloro-5-acetoxy-1-naphthol (I).

Wheeler and Mattox (2) obtained a trichloro compound by chlorinating 1,5-diacetoxynaphthalene at 50°, and also by further chlorination of the dichloro derivative at 80°. It has now been found that 1,5-diacetoxynaphthalene readily takes up three atoms of chlorine at room temperature in the presence of pyridine. The ease of substitution under these conditions was demonstrated when, in error, an experiment was carried out using only two-thirds of the amount of chlorine

required by theory. A 40% yield of the trichloro compound was obtained. Oxidation of the trichloro compound (II) with chromic acid yielded the quinone (III), but the structure 4,4,8-trichloro-5-acetoxy-1-hydroxy-3,4-dihydronaphthalene allotted to (II) by Wheeler and Mattox is considered incorrect for the following reasons:—the compound contains no free hydroxyl group, refluxing with aqueous alcohol removes two atoms of chlorine to give the quinone (III),² and condensation with two molecules of aniline removes all three chlorine atoms with formation of 2-anilino-5-acetoxy-1,4-naphthoquinone-4-anil (VII). The behavior of this substance is closely analogous to the trichloro compound obtained by chlorination of α -naphthol (6), and its structure is therefore regarded as 2,4,4-trichloro-5-acetoxy-1-keto-1,4-dihydronaphthalene (II). Reaction with phenylhydrazine yielded (I) as the main product, although there were indications of phenylhydrazone formation.

Chlorination of 5-acetoxy-1-methoxynaphthalene afforded a dichloro derivative identical with the product obtained by methylation of (I) with diazomethane. This compound is therefore 2,4-dichloro-5-acetoxy-1-methoxynaphthalene, yielding on hydrolysis, followed by methylation, 2,4-dichloro-1,5-dimethoxynaphthalene.

As bromination of 1,5-dimethoxynaphthalene yields the 4,8-dibromo derivative (3), an attempt was made to obtain authentic 4,8-dichloro-1,5-dihydroxynaphthalene by chlorination of 1,5-dimethoxynaphthalene, followed by demethylation. Treatment of 1,5-dimethoxynaphthalene with phosphorus pentachloride afforded mono- and di-chloro compounds. The former was shown to be the 4-chloro derivative by preparation of the identical compound from 4-amino-1,5-dimethoxynaphthalene by a Sandmeyer reaction, and hence the latter must be either the 4,6- or the 4,8-dichloro derivative, as it differs from the 2,4-isomer obtained by hydrolysis of (I), followed by methylation. To distinguish between the two possibilities, the dipole moments of 1,5-dimethoxynaphthalene and of the dichloro compound were measured and found to be 0.36D and 0.73D respectively.³ The similarity of these values indicates that the dichloro compound has the symmetrical structure 4,8-dichloro-1,5-dimethoxynaphthalene, but unfortunately attempts to demethylate this with hydriodic acid and with aluminum chloride were unsuccessful.

EXPERIMENTAL^{4, 5, 6}

Where identity is specified, this was established by mixed m.p.

2,4-Dichloro-5-acetoxy-1-naphthol (I). This was first prepared by the method of Wheeler and Mattox (2) but the following procedure was found more convenient: a suspension of 10

² As reported by Wheeler and Mattox (2) this reaction does not proceed with absolute alcohol.

³ As the significance of these absolute values is being considered, polarization data on these and further compounds will be published separately.

⁴ Melting points are uncorrected.

⁵ Microanalyses were carried out by Drs. G. Weiler and F. B. Strauss of Oxford, and Dr. J. W. Minnis of Edinburgh.

⁶ The author is indebted to Imperial Chemical Industries, Ltd., Dyestuffs Division, for a gift of 1,5-dihydroxynaphthalene.

g. of 1,5-diacetoxynaphthalene in 100 cc. of glacial acetic acid was stirred and 6 g. of chlorine passed in slowly. The solution was allowed to stand for two hours, heated to 80°, 50 cc. of hot water added and the solution then cooled rapidly in ice with stirring. The crystals which separated were recrystallized from aqueous acetic acid (100 cc. of glacial acetic acid + 50 cc. of water) in colorless needles, m.p. 159–160°, turning green; yield, 5.8 g., 52%.

Oxidation of this substance with chromic acid as described by Wheeler and Mattox afforded 2-chloro-5-acetoxy-1,4-naphthoquinone (III), yellow needles, m.p. 143°. Hydrolysis of (I) as directed by the same authors yielded 2,4-dichloro-1,5-dihydroxynaphthalene, m.p. 194°. A faintly alkaline dilute aqueous solution of this naphthol gave an immediate blue-violet coloration with 2,6-dichloroquinone-4-chloroimide (5).

2,4,4-Trichloro-5-acetoxy-1-keto-1,4-dihydronaphthalene (II). This was obtained from 1,5-diacetoxynaphthalene and from (I) by the method of Wheeler and Mattox but the following procedure was preferred. A suspension of 2.4 g. of 1,5-diacetoxynaphthalene in 25 cc. of glacial acetic acid containing 3.75 cc. of pyridine was stirred and 2.1 g. of chlorine passed in slowly. After standing overnight, the crystals which separated were collected and recrystallized from ligroin (b.p. 100–120°) in colorless needles, m.p. 174°; yield, 1.8 g., 60%.

Anal. Calc'd for $C_{12}H_7Cl_3O_3$: C, 47.1; H, 2.3; Cl, 34.85.

Found C, 47.3; H, 2.3; Cl, 34.7.

Reactions of (II).

(a) *With chromic acid.* Oxidation as for (I) yielded the quinone (III).

(b) *With aqueous alcohol.* One gram of (II) was refluxed for one hour with 40 cc. of alcohol and 20 cc. of water. The solution was then cooled, filtered, and 50 cc. of water added. Crystallization of the yellow precipitate obtained, from alcohol, yielded 0.4 g. of the quinone (III).

(c) *With aniline.* To a hot solution of 2 g. of (II) in 60 cc. of alcohol, 3 g. of aniline in 10 cc. of alcohol was added. After refluxing for one hour the solution was allowed to stand overnight, and the crystals which separated were collected and recrystallized from acetone (charcoal). 2-Anilino-5-acetoxy-1,4-naphthoquinone-4-anil (VII) separated in small lustrous reddish-brown plates, m.p. 212°.

Anal. Calc'd for $C_{24}H_{18}N_2O_3$: N, 7.3. Found: N, 7.35.

(d) *With phenylhydrazine.* To a solution of 1.5 g. of (II) in 50 cc. of alcohol, 1 g. of phenylhydrazine hydrochloride in 10 cc. of water containing 1.5 g. of sodium acetate was added. After warming for thirty minutes on the steam-bath, the red solution was cooled, and diluted with 100 cc. of water. A light red precipitate was obtained, and this after two crystallizations from dilute acetic acid (charcoal) yielded 1 g. of the dichloro compound (I). The red color indicated some phenylhydrazone formation but this was not isolated.

2,3-Dichloro-5-acetoxy-1,4-naphthoquinone (IV). This was obtained by chlorination of the quinone (III) as described by Wheeler and Mattox (2) who regarded it as the 2,8-isomer. It separated from alcohol in yellow plates or needles (according to the rate of cooling), m.p. 158–159°. The identical compound was prepared by acetylation of 2,3-dichlorojuglone. One-half gram of 2,3-dichlorojuglone was refluxed gently for one hour with 7.5 cc. of acetic anhydride containing one drop of concentrated sulfuric acid. The solution was then cooled, poured onto crushed ice, and the precipitate so obtained crystallized from alcohol in yellow plates, m.p. 158–159°. This is a modification of the procedure of Wheeler and Scott (4) who reported 2,3-dichlorojuglone m.p. 149°, and acetate m.p. 154°. Wheeler and Naiman (8) later reported m.p. 153° for 2,3-dichlorojuglone but did not acetylate their product. 2,3-Dichlorojuglone obtained by the present author had m.p. 154°.

3-Anilino-2-chloro-5-acetoxy-1,4-naphthoquinone (VI). This was prepared by the method of Wheeler and Mattox (2) who regarded it as the 2-anilino-8-chloro isomer, and the identical compound was obtained by refluxing 0.8 g. of (IV) with 0.3 g. of aniline in 60 cc. of alcohol for thirty minutes. Red needles separated on cooling, m.p. 172°.

4-Chloro-1,5-dimethoxynaphthalene. (a) A mixture of 3.1 g. of 1,5-dimethoxynaphthalene and 3.7 g. of phosphorus pentachloride was warmed on the steam-bath for twenty

minutes. The dark liquid which formed solidified on cooling and was ground with water and filtered. The solid consisted of a mixture of mono- and di-chloro compounds which were separated by fractional crystallization from glacial acetic acid, the monochloro derivative being the more soluble. Final purification of 4-chloro-1,5-dimethoxynaphthalene is best achieved by crystallization from ligroin (b.p. 100–120°) or dilute methyl alcohol. It forms colorless leaflets, m.p. 122°; yield, 0.5 g., 14%.

Anal. Calc'd for $C_{12}H_{11}ClO_2$: C, 64.7; H, 4.9; N, 15.95.

Found: C, 65.0; H, 5.0; N, 16.0.

(b) Four and one-half grams of 4-amino-1,5-dimethoxynaphthalene hydrochloride (7) was boiled with 75 cc. of water and 5 cc. of concentrated hydrochloric acid, and cooled rapidly in ice. A solution of 1.4 g. of sodium nitrite in 50 cc. of water was added slowly below the surface at 0–5°. After ten minutes the diazo solution was filtered and then added in portions to an ice-cold solution of 3 g. of cuprous chloride in 18 cc. of concentrated hydrochloric acid, and the mixture warmed on the steam-bath for one hour until the evolution of nitrogen ceased. The product was collected, washed with water, dried, and extracted with ligroin (b.p. 50–60°). The extract was treated with charcoal and concentrated to small bulk. The crystals which separated were recrystallized from dilute alcohol in leaflets, m.p. 122° identical with the product from (a) above; yield, 0.7 g., 17%.

4,8-Dichloro-1,5-dimethoxynaphthalene. This was prepared from 3.1 g. of 1,5-dimethoxynaphthalene, and 7.5 g. of phosphorus pentachloride by procedure (a) given above for the 4-chloro derivative. Crystallization from glacial acetic acid (charcoal) afforded colorless plates, m.p. 157°; yield, 2.3 g., 54%.

Anal. Calc'd for $C_{12}H_{10}Cl_2O_2$: C, 56.0; H, 3.9; Cl, 27.6.

Found: C, 55.9; H, 4.0; Cl, 28.1.

2,4-Dichloro-5-acetoxy-1-methoxynaphthalene. (a) A solution of 2.1 g. of 5-acetoxy-1-methoxynaphthalene in 10 cc. of glacial acetic acid was stirred at room temperature and 1.4 g. of chlorine was passed in slowly. After one hour the solution was poured onto ice, yielding an oil which solidified on standing. The solid was collected, washed with water, dried, and extracted with ligroin (b.p. 30–40°). The extract was evaporated to dryness and the residue crystallized from dilute acetic acid forming colorless needles, m.p. 112°; yield, 1.0 g., 29%.

Anal. Calc'd for $C_{13}H_{10}Cl_2O_3$: C, 54.7; H, 3.5; Cl, 24.9.

Found: C, 54.8; H, 3.5; Cl, 25.3.

(b) Three grams of 2,4-dichloro-5-acetoxy-1-naphthol in a solution of 50 cc. of ether and 50 cc. of chloroform at -10° , was methylated with diazomethane obtained by the action of 10 cc. of 50% potassium hydroxide solution on 5 g. of nitrosomethylurea in 30 cc. of ether. The ether was allowed to evaporate at room temperature and the chloroform solution then concentrated to small bulk. Crystals separated on cooling, and these when recrystallized from dilute acetic acid afforded colorless needles, m.p. 112° identical with the product of (a) above; yield, 2.2 g., 70%.

2,4-Dichloro-1-methoxy-5-naphthol. A solution of 1 g. of 2,4-dichloro-5-acetoxy-1-methoxynaphthalene in 50 cc. of alcohol was refluxed with 20 cc. of concentrated hydrochloric acid for two hours. The cooled solution was poured into 100 cc. of water, and the product collected and crystallized from dilute methyl alcohol. It separated in colorless needles m.p. 80°; yield, 0.6 g., 70%.

Anal. Calc'd for $C_{11}H_8Cl_2O_2$: C, 54.3; H, 3.3; Cl, 29.2.

Found: C, 54.0; H, 3.6; Cl, 29.2.

2,4-Dichloro-1,5-dimethoxynaphthalene. A solution of 2.5 g. of 2,4-dichloro-1,5-dihydroxynaphthalene in 100 cc. of ether was methylated with diazomethane at -10° . The ether was allowed to evaporate at room temperature and the oily residue distilled at 10 mm. pressure. The solid distillate crystallized from dilute methyl alcohol in colorless needles, m.p. 74–75°; yield, 0.8 g., 36%.

Anal. Calc'd for $C_{12}H_{10}Cl_2O_2$: C, 56.0; H, 3.9; Cl, 27.6.

Found: C, 55.8; H, 3.9; Cl, 27.6.

Acknowledgment. The author is indebted to Dr. Ernst Bergmann of the Daniel Sieff Research Institute, Rehovoth, Palestine, for suggesting the aid of dipole moments, and to Dr. E. L. Sutton of Magdalen College, Oxford, for the dipole moment determinations.

SUMMARY

The di- and tri-chloro derivatives obtained by chlorination of 1,5-diacetoxynaphthalene have been reinvestigated and identified as 2,4-dichloro-5-acetoxy-1-naphthol and 2,4,4-trichloro-5-acetoxy-1-keto-1,4-dihydronaphthalene respectively.

Chlorination of 1,5-dimethoxynaphthalene yields 4-chloro- and 4,8-dichloro-1,5-dimethoxynaphthalene.

Chlorination of 5-acetoxy-1-methoxynaphthalene yields 2,4-dichloro-5-acetoxy-1-methoxynaphthalene.

ABERDEEN, SCOTLAND

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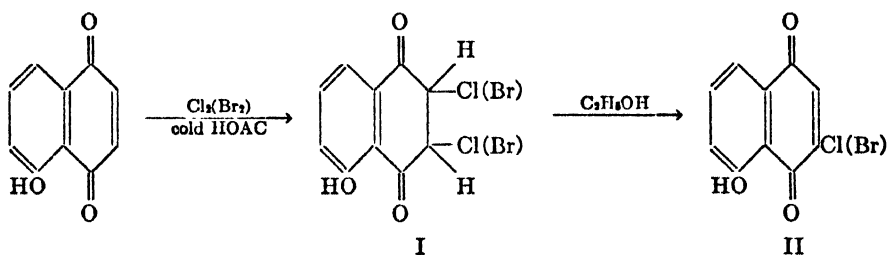
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STUDIES IN THE JUGLONE SERIES. I. SOME HALOGEN DERIVATIVES AND THEIR REACTION WITH ANILINE

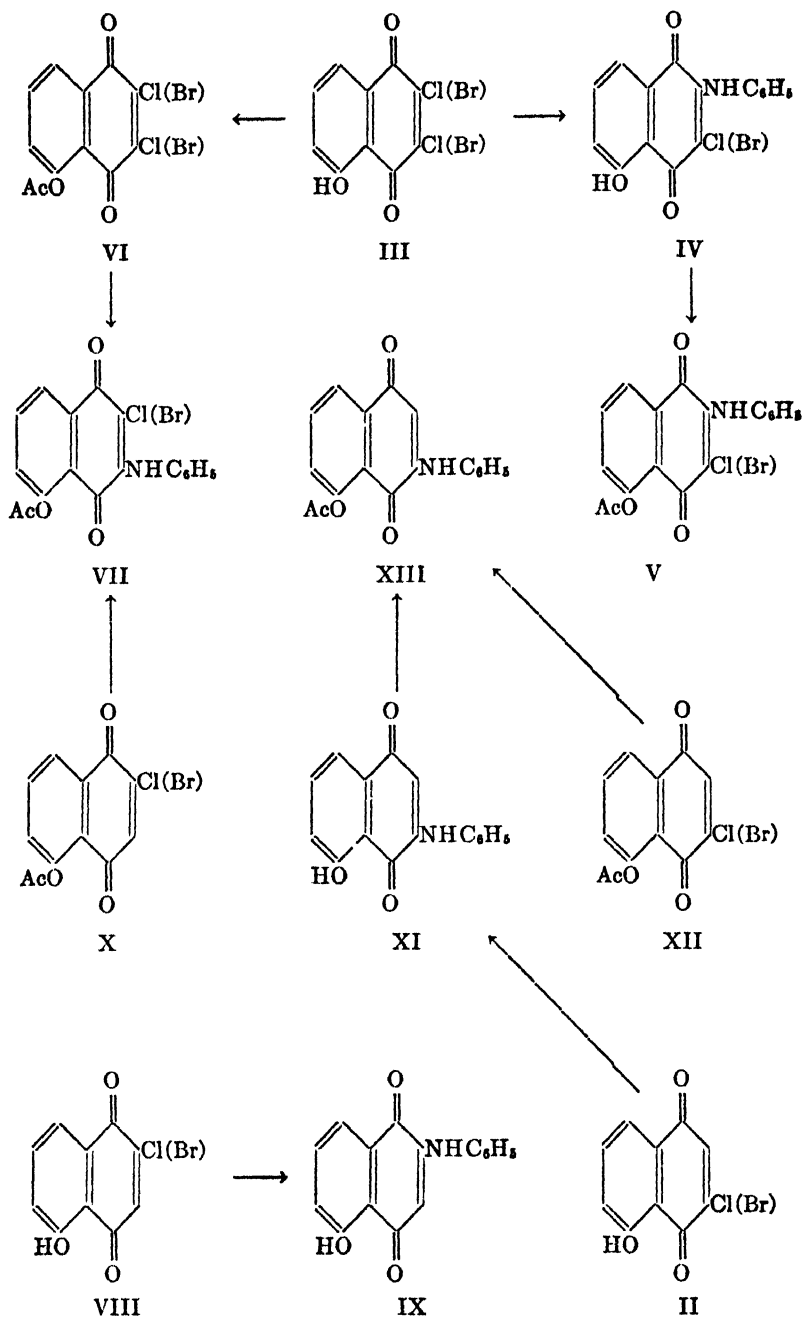
R. H. THOMSON

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Juglone was first isolated by Vogel and Reischauer (1) in 1856, from fresh walnut shells (*Juglans regia*), where it occurs as an α -hydrojuglone. In 1885 it was shown by Bernthsen and Semper (2) to have the structure 5-hydroxy-1,4-naphthoquinone, which was confirmed two years later by the same authors when they synthesized juglone by chromic acid oxidation of 1,5-dihydroxynaphthalene (3). The chemistry of juglone has not been greatly expanded since that time, and the derivatives which have been obtained are, in many cases, of uncertain constitution. Thus the preparation, by two different methods, of the acetates of 2-chloro- and 2-bromo-juglone is reported in the literature. The brief descriptions accorded to these compounds however, are not in agreement, the difference in melting point amounting to 10° in the case of the bromo derivative, and since the structure of these substances was only assumed by one group of workers, it seemed desirable to verify their identity. In the course of this work it was observed that the constitutions assigned to a number of halogeno-juglones in the literature were not well established and certain of these have also been re-examined.



2-Chloro- and 2-bromo-juglone were first obtained by Wheeler and Scott (4) by treating juglone in cold glacial acetic acid solution with the appropriate halogen to yield a dihalide addition product (I), which readily splits off a molecule of halogen acid on warming with alcohol. It is clear that the halogen atom in the monohalogenojuglone so obtained may be located at either position 2 or position 3, and in fact a mixture of two isomers would be anticipated. Wheeler and co-workers however, obtained only one isomer in each case, and this they assumed to be the 2-halogeno derivative. The acetates were derived in the usual way. The acetate of 2-bromojuglone was also prepared by Carter, Race, and Rowe (6) by chromic acid oxidation of 2,4-dibromo-5-acetoxy-1-naphthol, a method which admits of no ambiguity, and Thomson (7) has shown that the acetate of 2-chlorojuglone can be obtained in the same way from 2,4-dichloro-5-acetoxy-1-naphthol. These compounds have now been prepared by both



methods, and it has been found that the acetates of Wheeler and Scott (**XII**) are different from those of Carter *et al.*, and of Thomson (**X**), the latter yielding on hydrolysis 2-chloro- and 2-bromo-juglones (**VIII**) different from those of Wheeler and Scott (**II**). Hence the products obtained by elimination of a molecule of

halogen acid from juglone dichloride and dibromide must be the 3-chloro- and 3-bromo-juglones (II). 3-Halogenojuglones have been obtained in this way in high yield but no trace of the 2-isomers has been found, and if formed at all must be in negligible amounts. This exclusive formation of the 3-isomers is rather surprising and must be ascribed to the effect of the hydroxyl group in the benzenoid ring. It may be noted in this connection that Fieser and Dunn (8) observed that the presence of hydroxyl groups in the benzenoid ring of α -naphthoquinone had a marked influence on the additive power of the ethylenic linkage in the quinonoid ring.

Further chlorination of both 2- and 3-chlorojuglone yields 2,3-dichlorojuglone, whilst further bromination of the two bromo compounds yields 2,3-dibromojuglone, which, as was shown by Wheeler and Naiman (5) is readily converted by alcoholic hydrochloric acid to the 2,3-dichloro compound. These reactions firmly establish the constitutions of the 2,3-dihalogenojuglones.

By direct bromination of juglone, Wheeler and Scott (4) obtained a tribromo derivative. One of the bromine atoms was reactive, due, it was thought, to its position para to the hydroxyl group, and the compound was therefore regarded as 2,3,8-tribromojuglone (9). The same compound has now been obtained by further bromination of 2,3-dibromojuglone and 2,6-dibromojuglone, and its structure is therefore 2,3,6-tribromojuglone. The reactions of this compound will be considered further in a subsequent paper.

2,3-Dichlorojuglone (III) reacts readily with aniline and certain other arylamines, with replacement of one of the chlorine atoms, and it was assumed by Wheeler, Dawson, and McEwen (10) that the products were 2-arylamino-3-chlorojuglones (IV). It is known that reaction of 2,3-dichlorojuglone acetate (VI) with aniline affords 3-anilino-2-chlorojuglone acetate (VII) since the same compound can be obtained by reaction of aniline with 2-chlorojuglone acetate (X) (7). Comparison of this acetate (VII) with the acetate (V) of (IV) has shown that these are different compounds which thus confirms the structure originally assigned to (IV). It therefore appears that in 2,3-dichlorojuglone the chlorine atom at position 2 is reactive, whereas in 2,3-dichlorojuglone acetate the chlorine atom at position 3 is reactive. Similarly reaction of 2,3-dibromojuglone with aniline affords 2-anilino-3-bromojuglone, but if the reaction is preceded by acetylation of the hydroxyl group, the product is the acetate of 3-anilino-2-bromojuglone.

These unexpected results led to an examination of the reaction of the monohalogenojuglones and their acetates with aniline. 2-Chloro- and 2-bromojuglone (VIII), and 3-chloro- and 3-bromo-juglone (II), all react with elimination of the halogen atom to form the corresponding 2- and 3-anilinojuglones (IX), (XI). One of these corresponds to the anilinojuglone obtained by Mylius (11) from hydroxyjuglone, but their identity has not yet been established. Attempts to make an anilinojuglone by direct reaction of juglone and aniline failed, in contrast to α -naphthoquinone (12) and 5-chloro and 5-bromo-naphthoquinone (13), which readily form anilino derivatives. The acetates of the 2-halogenojuglones (X) yield 3-anilino-2-halogenojuglone acetates (VII), but in the case

of the acetates of the 3-halogenojuglones (XII) the halogen atom is again eliminated to give the acetate of 3-anilinojuglone (XIII), the bromo compound forming, in addition, a small amount of 2-anilino-3-bromojuglone acetate (V). The product obtained from the reaction of 3-chlorojuglone acetate and aniline appeared to be very similar to that obtained from the corresponding bromo compound but it was not found possible to isolate 2-anilino-3-chlorojuglone acetate.

It is clear from the behavior of these compounds that the substituent in the benzenoid ring has a pronounced influence on the reaction taking place in the quinonoid ring; when the benzenoid ring is unsubstituted, as in 2-chloro- and 2-bromo-1,4-naphthoquinone, the halogen atom is not replaced and reaction with aniline affords 3-anilino-2-chloro- or -bromo-1,4-naphthoquinone (14). On the other hand 2,6-dichloro-1,4-naphthoquinone reacts with aniline to give 2-anilino-6-chloro-1,4-naphthoquinone (15), and 2,6-dibromo- and 2,6,8-tribromo-juglone yield 2-anilino-6-bromo- and 2-anilino-6,8-dibromo-juglone respectively (16). From the information at present available it appears, therefore, that with the exception of the acetoxy group at position 5, substitution in the benzenoid ring favors halogen replacement in the quinonoid ring, but until more data have been obtained it is difficult to find any comprehensive explanation of these anomalous reactions.

EXPERIMENTAL^{1, 2, 3}

Where identity is specified this was established by mixed m.p.

3-Chloro- and 3-bromo-juglone (II). These were prepared by the method of Wheeler and Scott (4) and the improved method of Wheeler and Naiman (5). The dihalide addition products were converted to the monohalogenojuglones most expeditiously by boiling one part dihalide with six parts alcohol for three or four minutes until crystals began to separate. The suspension was then cooled and the crystals collected. 3-Chlorojuglone was obtained in 83% yield from the dichloride; orange needles from alcohol, m.p. 166°. The acetate crystallized from alcohol in yellow plates, m.p. 147°. 3-Bromojuglone was obtained in 98% yield from the dibromide; orange-brown leaflets or needles from glacial acetic acid, m.p. 172°. The acetate crystallized from alcohol in yellow plates, m.p. 151.5°. (Wheeler and Scott report m.p. 166°, and acetate, m.p. 148°.)

Wheeler and co-workers prepared the acetates of several halogenojuglones by heating with a large excess of acetic anhydride for several hours. This lengthy procedure is not necessary. The acetates are readily prepared by boiling one part halogenojuglone with two or three parts acetic anhydride, containing a trace of concentrated sulfuric acid, for one minute. The acetyl derivatives separate rapidly on cooling.

2-Chloro- and 2-bromo-juglone (VIII). 2-Chlorojuglone acetate was prepared by oxidation of 2,4-dichloro-5-acetoxy-1-naphthol according to the procedure of Wheeler and Mattox (17), who erroneously regarded the substance as the acetate of 8-chlorojuglone (7); yellow needles, m.p. 143°. A mixture with the acetate of 3-chlorojuglone had m.p. 116–120°. Hydrolysis with alcoholic hydrochloric acid yielded 2-chlorojuglone, orange-brown plates from alcohol, m.p. 112°.

¹ Melting points are uncorrected.

² Microanalyses were carried out by Drs. G. Weiler and F. B. Strauss of Oxford, and Dr. J. W. Minnis of Edinburgh.

³ The author is indebted to Imperial Chemical Industries Ltd., Dyestuffs Division, for a gift of 1,5-dihydroxynaphthalene, from which juglone was prepared.

2-Bromojuglone acetate was prepared by oxidation of 2,4-dibromo-5-acetoxy-1-naphthol as described by Carter *et al.* (6), yellow needles, m.p. 158°. A mixture with the acetate of 3-bromojuglone had m.p. 124–126°. 2-Bromojuglone was obtained by hydrolysis with alcoholic sulfuric acid. Hydrolysis with hydrochloric acid yields 2-chlorojuglone, which is in consonance with the known lability of the bromine atoms in 3-bromo- and 2,3-dibromojuglone. A solution of 2 g. of 2-bromojuglone acetate in 80 cc. of alcohol was refluxed for one hour with a solution of 4 cc. of concentrated sulfuric acid in 20 cc. of water. The crystals which separated on cooling were recrystallized twice from acetone and finally from ligroin (b.p. 50–60°); orange-red prisms, m.p. 136°; yield, 87%.

Anal. Calc'd for $C_{10}H_7BrO_3$: C, 47.4; H, 2.0; Br, 31.6.

Found: C, 47.5; H, 2.2; Br, 31.9.

2,3-Dichlorojuglone (III). A solution of either 2- or 3-chlorojuglone in a little glacial acetic acid containing a 50% excess of chlorine was heated for three hours on the steam-bath. Crystals of 2,3-dichlorojuglone separated on cooling. Recrystallization from alcohol gave golden-brown needles, m.p. 154°.

2,3-Dibromojuglone (III). This was prepared in the same manner as the dichloro compound from either 2- or 3-bromojuglone. Recrystallization from alcohol yielded golden-brown needles, m.p. 169°.

2,3,6-Tribromojuglone. This was obtained by direct bromination of juglone by the method of Wheeler and Scott (4), who regarded it as the 2,3,8-isomer, and also by bromination of 2,3-dibromojuglone and 2,6-dibromojuglone (6, 16). To a hot solution of 0.8 g. of dibromojuglone in 10 cc. of glacial acetic acid, was added a solution of 0.2 cc. of bromine in 2 cc. of glacial acetic acid. After warming for three hours on the water-bath the solution was allowed to cool, when red needles were deposited. These had m.p. 172° which was not raised by further crystallization. The identical product was obtained from all three sources, each yielding an identical acetate, yellow needles, m.p. 188°. (Wheeler and Scott report m.p. 170°, and acetate, m.p. 186°.)

2-Anilino-3-chlorojuglone acetate (V). A solution of 0.8 g. of 2-anilino-3-chlorojuglone (10) in 8 cc. of pyridine was refluxed for one hour with 2.5 cc. of acetic anhydride, cooled, and poured onto crushed ice. The red precipitate so obtained was collected and recrystallized twice from alcohol; fine rust-red needles, m.p. 183°; yield, 88%.

Anal. Calc'd for $C_{18}H_{12}ClNO_4$: C, 63.2; H, 3.5; Cl, 10.4; N, 4.1.

Found: C, 63.5; H, 3.6; Cl, 10.3; N, 4.2.

3-Anilino-2-chlorojuglone acetate (VII). This was prepared by reaction of aniline with the acetates of 2-chloro- and 2,3-dichloro-juglone (7); red needles, m.p. 172°. A mixture with (V) had m.p. 150–153°.

2-Anilino-3-bromojuglone (IV). To 0.8 g. of 2,3-dibromojuglone dissolved in 70 cc. of alcohol, 0.25 cc. of aniline was added, and the solution refluxed for twenty minutes. The orange solution rapidly became a dark violet-brown and crystals deposited on cooling. Recrystallization from acetone yielded dark violet needles (ruby by transmitted light), m.p. 215°; yield, 60%.

Anal. Calc'd for $C_{18}H_{10}BrNO_3$: C, 55.8; H, 2.9; Br, 23.25; N, 4.1.

Found: C, 56.15; H, 3.0; Br, 22.6; N, 4.3.

2-Anilino-3-bromojuglone acetate (V). A solution of 0.6 g. of 2-anilino-3-bromojuglone in 10 cc. of pyridine was warmed on the steam-bath with 1.5 cc. of acetic anhydride for ten minutes, and set aside for twenty-four hours. Crushed ice was then added to the solution to precipitate a red crystalline solid which had m.p. 203°. Recrystallization from glacial acetic acid afforded light red needles, m.p. 205°; yield, 80%.

Anal. Calc'd for $C_{18}H_{12}BrNO_4$: C, 56.0; H, 3.1; Br, 20.7; N, 3.6.

Found: C, 55.9; H, 2.8; Br, 20.2; N, 3.7.

3-Anilino-2-bromojuglone acetate (VII). A solution of 0.4 g. of 2,3-dibromojuglone acetate in 20 cc. of alcohol was refluxed with 0.1 cc. of aniline, the orange solution rapidly becoming deep red. After one hour the solution was concentrated to 10 cc. and allowed to

cool. The red solid which deposited was crystallized twice from alcohol to yield red needles, m.p. 162°; yield, 51%.

Anal. Calc'd for $C_{18}H_{12}BrNO_4$: C, 56.0; H, 3.1; Br, 20.7; N, 3.6.

Found: C, 56.3; H, 3.2; Br, 20.5; N, 3.4.

The same compound was also obtained by refluxing a solution of 0.8 g. of 2-bromojuglone acetate in 20 cc. of alcohol with 0.3 cc. of aniline for one hour.

2-Anilinojuglone (IX). A solution of 0.6 g. of 2-chlorojuglone in 30 cc. of alcohol was refluxed for ten minutes with 0.25 cc. of aniline. Crystals began to separate from the solution after four or five minutes. These were collected after cooling, and recrystallized from benzene in dark reddish-violet needles, m.p. 247°; yield, 63%. The same compound was obtained by reaction of 2-bromojuglone with aniline.

Anal. Calc'd for $C_{18}H_{11}NO_3$: C, 72.5; H, 4.2; N, 5.3.

Found: C, 72.6; H, 4.3; N, 5.4.

Acetylation with acetic anhydride in pyridine afforded an acetate separating from alcohol in fine red needles, m.p. 204°.

Anal. Calc'd for $C_{18}H_{13}NO_4$: C, 70.4; H, 4.2; N, 4.55.

Found: C, 70.4; H, 4.4; N, 4.25.

3-Anilinojuglone (XI). A solution of 1.2 g. of 3-chlorojuglone in 80 cc. of alcohol was refluxed with 0.6 cc. of aniline for one hour. The dark crystalline solid which separated on cooling was dissolved in 100 cc. of hot acetone, filtered from a little black insoluble material, and concentrated to small bulk. The crystals obtained, when recrystallized from acetone (charcoal) formed small russet leaflets, m.p. 228°; yield, 52%.

Anal. Calc'd for $C_{18}H_{11}NO_3$: C, 72.5; H, 4.2; N, 5.3.

Found: C, 72.35; H, 4.25; N, 5.4.

Acetylation with acetic anhydride in pyridine afforded an acetate (XIII), crystallizing from alcohol in red needles, m.p. 168°.

Anal. Calc'd for $C_{18}H_{13}NO_4$: C, 70.4; H, 4.2; N, 4.55.

Found: C, 70.1; H, 4.25; N, 4.75.

An anilinojuglone is reported by Mylius (11), m.p. 230°, but the identity of these compounds has not yet been established. When attempts were made to prepare an anilinojuglone by refluxing a solution of 1 g. of juglone in 60 cc. of alcohol with 0.5 cc. of freshly distilled aniline, extensive decomposition occurred in a few minutes. A black solid separated, from which nothing could be obtained by solvent extraction. Variation of this procedure had the same result.

Reactions of monohalogenojuglone acetates with aniline. (a) *2-Chloro- and 2-bromojuglone acetates (X).* These give the corresponding 3-anilino-2-chloro- or -bromojuglone acetates (VII) (see above).

(b) *3-Chlorojuglone acetate (XII).* A solution of 1 g. of 3-chlorojuglone acetate in 20 cc. of alcohol was refluxed with 0.4 cc. of aniline for one hour. The solution was then concentrated to half bulk and allowed to stand overnight. Dark red crystals (0.4 g.) were deposited, m.p. 140–143°. Recrystallization from benzene yielded red needles, m.p. 168°, identical with the acetate of 3-anilinojuglone (XIII). Attempts to isolate an anilinochlorojuglone acetate by fractional crystallization and by chromatographic separation were unsuccessful.

(c) *3-Bromojuglone acetate (XII).* A solution of 0.9 g. of 3-bromojuglone acetate in 15 cc. of alcohol was refluxed for one hour with 0.3 cc. of aniline, and then allowed to stand overnight. A dark red solid (0.4 g.) separated from the solution, m.p. 147–150°. Crystallization from the minimum amount of glacial acetic acid yielded a small crop (50 mg.) of red needles, m.p. 204°. Hot water was added to the mother liquor and the solution allowed to crystallize. Red needles (0.25 g.) separated, m.p. 162°. Recrystallization of the first crop from glacial acetic acid afforded fine light red needles, m.p. 205°, identical with 2-anilino-3-bromojuglone acetate (V). Recrystallization of the second crop once from dilute acetic acid, and twice from alcohol furnished red needles, m.p. 168°, identical with the acetate of 3-anilinojuglone (XIII).

SUMMARY

Compounds prepared from juglone *via* intermediate addition products and hitherto described as 2-chloro- and 2-bromo-juglone have been re-orientated as 3-chloro- and 3-bromo-juglone.

A tribromo derivative obtained by direct bromination of juglone has been shown to be the 2,3,6- and not the 2,3,8-isomer.

The reactions of aniline with certain halogenojuglones have been investigated.

ABERDEEN, SCOTLAND

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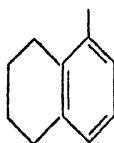
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THE DISSOCIATION RATES OF 1,1,1,2-TETRAPHENYL-2-ARYL-ETHANES CONTAINING TETRALYL, NAPHTHYL, FLUORYL, AND TETRAHYDROPHENANTHRYL GROUPS

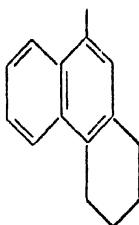
W. E. BACHMANN AND C. E. BROCKWAY¹

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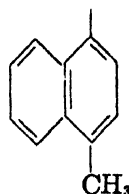
The present paper is a continuation of the study of the rates of dissociation of pentaarylethanes (1, 2, 3). Six new pentaarylethanes of the type $(C_6H_5)_3C-CH(C_6H_5)R$ have been synthesized in which R is 5,6,7,8-tetrahydro-1-naphthyl (I), 1,2,3,4-tetrahydro-9-phenanthryl (II), 4-methyl-1-naphthyl (III), 4-fluoryl (IV), 5,6,7,8-tetrahydro-2-naphthyl (V), and 1-fluoryl (VI). The rate constants (k) and half-life periods ($t_{1/2}$) of these 1,1,1,2-tetraphenyl-2-arylethanes in the reaction with iodine (2) at 80° have been determined; the values for these constants are shown beneath the formulas for the groups (for R = phenyl; $k = 0.0124$; $t_{1/2} = 56$ min.).



I
 $k = 0.0728$
 $t_{1/2} = 9.5$ min.

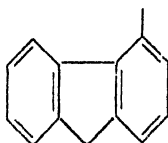


II
 $k = 0.0681$
 $t_{1/2} = 10.1$ min.

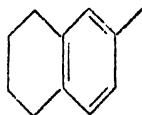


III
 $k = 0.0598$
 $t_{1/2} = 11.6$ min.

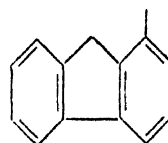
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IV
 $k = 0.0432$
 $t_{1/2} = 16$ min.



V
 $k = 0.0190$
 $t_{1/2} = 36$ min.



VI
 $k = 0.0161$
 $t_{1/2} = 43$ min.

The effect of the 1-tetralyl group is of the same order but somewhat greater than that of the *o*-tolyl group; likewise, the effect of the 2-tetralyl group is of the same order but greater than that of the *m*-tolyl group. Recently, Grunert, Nichol, and Sandin (4) determined the effect of some xyllyl groups.² The

¹ From the Ph.D. dissertation of Charles E. Brockway, June 1944. Present address: Goodrich Rubber Company, Akron, Ohio.

² It is of interest that by combining the effects of the single methyl groups in the *o*-, *m*- ($t_{1/2} = 41$) and *p*- positions one arrives at values for the effects (expressed in terms of the half-life periods of the corresponding 1,1,1,2-tetraphenyl-2-arylethanes) of the dimethylphenyl

1-tetralyl group (I) shows a somewhat greater effect than the 2,3-dimethylphenyl group ($t_1 = 13.4$) and, similarly, the effect of the 2-tetralyl group (V) is greater than that of the 3,4-dimethylphenyl group ($t_1 = 46$). It will be of interest to determine the effect of the 2,6-dimethylphenyl, the *sym*-octahydroanthryl, and the 9-anthryl groups. Preliminary experiments along these lines have been initiated.

The greater effect of 4-methyl-1-naphthyl (III) compared to 1-naphthyl ($t_1 = 15.9$) is in qualitative agreement with the greater effect of *p*-tolyl ($t_1 = 52$) compared to phenyl ($t_1 = 56$). Likewise, the effect of the tetrahydrophenanthryl group II (which may be considered as a 3,4-disubstituted naphthyl group) is slightly greater than that of III. It is of interest that the effect of the 1-fluoryl group (VI) is less than that of the *o*-tolyl group ($t_1 = 22.2$) (3) and the 4-fluoryl group (IV) is less effective than the *o*-biphenyl group ($t_1 = 10.8$) (3).

EXPERIMENTAL

Reduction of ketones to hydrols. In most instances a mixture of the ketone (5 g.) and solid aluminum isopropoxide (4.5 g.) (5) in dry toluene (24 cc.) was refluxed for six to twelve hours. To the cooled solution was added 20–30 cc. of benzene and this was distilled slowly until the temperature reached 100°. After this operation had been repeated twice more, the cooled mixture was hydrolyzed with dilute acid. In the preparation of phenyltetrahydrophenanthrylcarbinol, xylene was employed, the mixture was refluxed for forty-eight hours and benzene distillation was not used.

Preparation of the bromides from the carbinols. The bromides were prepared by interaction of the carbinols and acetyl bromide (2). The liquids were removed, a solution of the product in benzene was heated with Norit, and the filtered solution was evaporated.

1-Benzoyl-5,6,7,8-tetrahydronaphthalene. Twenty grams of benzonitrile was added to the Grignard reagent prepared from 39 g. of 1-iodotetralin (6) and 3.6 g. of magnesium in 125 cc. of ether. After two hours of refluxing and stirring the mixture was poured onto a mixture of ice and ammonium chloride. When the ice had melted, the organic layer was separated and shaken with 150 cc. of 10% hydrochloric acid. The aqueous solution of the ketimine hydrochloride was separated and warmed for ninety minutes; during this time the ketone precipitated as a viscous liquid, which was purified by distillation; b.p. 135–140°/0.1 mm.; yield, 7.69 g. (22%).

Anal. Calc'd for $C_{17}H_{16}O$: C, 86.4; H, 6.8.

Found: C, 86.2; H, 6.5.

1,1,1,2-Tetraphenyl-2-(5',6',7',8'-tetrahydro-1'-naphthyl)ethane (I). Phenyl-1-tetralylcarbinol, prepared by the general method, was an uncrystallizable liquid; it gave a deep red-violet color with concentrated sulfuric acid. The corresponding bromide (4.5 g.), which was also obtained as a liquid, was added to a solution of triphenylmethylsodium prepared by shaking 3.42 g. of triphenylchloromethane in 50 cc. of anhydrous ether and 40 cc. of benzene with 5 cc. of 45% sodium amalgam (1). The pentaarylethane was obtained in colorless crystals from petroleum ether; yield, 4.09 g. (72%); m.p. in air, 193–195°; in vacuum, 195–198°.

Anal. Calc'd for $C_{36}H_{32}$: C, 93.1; H, 6.9.

Found: C, 93.0; H, 6.7.

groups which are of the same order as those (shown in brackets) determined by Grunert, Nichol, and Sandin: 2,3-, 17 [13.4]; 2,4-, 20 [21.3]; 2,5-, 17 [15]; 3,4-, 38 [46]; 3,5-, 30 [33]. On the same basis the half-life period of 1,1,1,2-tetraphenyl-2-*sym*-octahydrophenanthryl-ethane, which has not yet been prepared, would be expected to be about 6 minutes.

Phenyl-(1,2,3,4-tetrahydro-9-phenanthryl)carbinol. This carbinol was obtained in 77% yield by aluminum isopropoxide reduction of 9-benzoyl-1,2,3,4-tetrahydrophenanthrene (7). It was also prepared by adding a solution of 1.07 g. of 1,2,3,4-tetrahydrophenanthrene-9-aldehyde (7) in 15 cc. of benzene to the Grignard reagent prepared from 1.05 cc. of bromobenzene in 15 cc. of ether and refluxing for an hour. After hydrolysis and steam distillation of the mixture, the carbinol was crystallized from a mixture of ether and petroleum ether; yield, 0.59 g. (40%); m.p. 84.5–85°. The colorless carbinol gives a bright purple color with concentrated sulfuric acid.

Anal. Calc'd for $C_{21}H_{20}O$: C, 87.5; H, 6.9.

Found: C, 87.3; H, 6.9.

1,1,1,2-Tetraphenyl-2-(1',2',3',4'-tetrahydro-9'-phenanthryl)ethane (II). The liquid carbinol bromide obtained from 5.1 g. of the carbinol was added to 50 cc. of benzene, 3.72 g. of triphenylmethylchloride and 5 cc. of mercury, and the mixture was shaken in a nitrogen atmosphere for forty-eight hours (1). The pentaarylethane crystallized from 50 cc. of petroleum ether (60–75°) containing a little ether, in colorless platelets; yield, 3.92 g. (57%); m.p. in air, 170–179°; in a vacuum, 176–179°.

Anal. Calc'd for $C_{40}H_{34}$: C, 93.4; H, 6.6.

Found: C, 93.1; H, 6.7.

Phenyl-(4-methyl-1-naphthyl)carbinol. The carbinol obtained by reduction of 8.33 g. of 4-methyl-1-benzoylnaphthalene (8) crystallized from alcohol in colorless form; yield, 6.17 g.; m.p. 111–112°. It gives a deep purple color with concentrated sulfuric acid.

Anal. Calc'd for $C_{18}H_{18}O$: C, 87.1; H, 6.5.

Found: C, 86.9; H, 6.6.

1,1,1,2-Tetraphenyl-2-(4'-methyl-1'-naphthyl)ethane (III). Treatment of 2.88 g. of the aforementioned carbinol in benzene with dry hydrogen chloride gave the chloride, which did not crystallize. The chloride and 2.7 g. of triphenylchloromethane in 70 cc. of dry benzene were shaken with 2 cc. of mercury in a nitrogen atmosphere for forty-eight hours. The crude pentaarylethane was triturated with a few drops of absolute alcohol and then 25 cc. of petroleum ether and filtered; yield, 3.91 g. (83%); m.p. in air, 180–183°; in a vacuum, 186–189°. A 74% yield of the same product was obtained from the reaction between the chloride and triphenylmethylsodium. It crystallized from petroleum ether in tiny colorless prisms.

Anal. Calc'd for $C_{37}H_{30}$: C, 93.7; H, 6.3.

Found: C, 93.6; H, 6.5.

4-Benzoylfluorene. (a) *From 4-cyanofluorene.* A mixture of 10 g. of fluorene-4-carboxylic acid (9) and 20 cc. of thionyl chloride was refluxed for two and one-half hours. The excess thionyl chloride was removed by distillation, and a solution of the residual acid chloride in 20 cc. of warm acetone was added with stirring to 150 cc. of chilled concentrated aqueous ammonia. After ten minutes the colorless *fluorene-4-carbonamide* was filtered; yield, 9.74 g. (99%); m.p. 215–216°.

Anal. Calc'd for $C_{14}H_{11}NO$: N, 6.70. Found: N, 6.61; 6.70.

A mixture of 9 g. of the amide, 2 g. of powdered sodium chloride and 3 cc. of phosphorus oxychloride (10) was heated for fifteen minutes on a sand-bath. The *4-cyanofluorene*, isolated by distillation of the mixture under reduced pressure, crystallized from alcohol in small colorless platelets; yield, 6.6 g. (82%); m.p. 77–78°.

Anal. Calc'd for $C_{14}H_9N$: N, 7.33. Found: N, 7.20; 7.32.

A solution of 5 g. of 4-cyanofluorene in 30 cc. of benzene was added to the Grignard reagent prepared from 4.4 cc. of bromobenzene in 30 cc. of ether. After four hours of refluxing, the mixture was cooled and hydrolyzed with ice and ammonium chloride. When the organic layer was shaken with 100 cc. of 10% hydrochloric acid, a yellow precipitate of the ketimine hydrochloride (7.13 g.) separated; it was filtered, washed with ether, and then heated with 50 cc. of water and 8 cc. of concentrated hydrochloric acid in a sealed tube at 175–180° for twenty hours. The resulting *4-benzoylfluorene* was purified by distillation under reduced pressure and recrystallization from alcohol; yield, 3.64 g. (56%); m.p. 82–83°.

Anal. Calc'd for $C_{20}H_{15}O$: C, 88.9; H, 5.2.

Found: C, 88.7; H, 5.3.

(b) *From the acid chloride and phenylmagnesium bromide.* Pure acid chloride was prepared by vacuum distillation of the product obtained above, followed by recrystallization from 90–100° petroleum ether; m.p. 75°. A solution of the Grignard reagent from 6.8 cc. of bromobenzene, 1.58 g. of magnesium and 50 cc. of ether was added dropwise to a solution of 16.6 g. of the acid chloride in 160 cc. of benzene cooled by an ice-bath. After the mixture had stood at room temperature for fifteen hours, it was treated with 200 cc. of 10% aqueous potassium hydroxide and steam distilled for three hours. From the alkaline solution 4.84 g. of fluorene-4-carboxylic acid was recovered. The ketone was distilled under reduced pressure and crystallized from alcohol; yield, 9.81 g.; m.p. 82–83°.

Phenyl-4-fluorylcarbinol. The carbinol prepared in 76% yield by aluminum isopropoxide reduction of the ketone, was obtained in colorless crystals from petroleum ether (90–100°) containing a little alcohol; m.p. 104–105°.

Anal. Calc'd for $C_{20}H_{18}O$: C, 88.3; H, 5.9.

Found: C, 88.2; H, 6.0.

1,1,1,2-Tetraphenyl-2-(4'-fluoryl)ethane (IV). A mixture of 6.00 g. of crude phenyl-4-fluorylbromomethane and 4.87 g. of triphenylchloromethane in 100 cc. of benzene was shaken with 5 cc. of mercury for forty-eight hours. The colorless crystalline pentaarylethane was stirred with petroleum ether and filtered; yield, 7.1 g. (81%); m.p. in air 171–174°; in a vacuum, 176–179°.

Anal. Calc'd for $C_{30}H_{26}$: C, 94.0; H, 6.0.

Found: C, 93.6; H, 6.3.

2-Benzoyl-5,6,7,8-tetrahydronaphthalene. (a) *From tetralin.* A mixture of 28.4 cc. of benzoyl chloride and 32.6 g. of aluminum chloride was warmed until it formed a homogeneous liquid; after cooling it was dissolved in 183 cc. of carbon disulfide. To the solution 33 g. of tetralin was added slowly. After twelve hours at room temperature the mixture was refluxed for one-half hour, and then shaken with cold dilute sulfuric acid. The organic layer was washed twice with dilute alkali and with water, dried, and fractionated. A solution of the distillate (34.5 g.) in ether deposited fine colorless prisms of the ketone; yield, 28 g.; m.p. 40–41°. Scharwin (11) obtained the ketone as a liquid by addition of aluminum chloride to a carbon disulfide solution of benzoyl chloride and tetralin.

Anal. Calc'd for $C_{17}H_{16}O$: C, 86.4; H, 6.8.

Found: C, 86.5; H, 6.8.

(b) *From 5,6,7,8-tetrahydro-2-naphthoic acid.* The acid (m.p. 155–156°) was obtained in 52% yield by refluxing a mixture of 70 g. of 2-chloroacetyltetralin (12) and 3.5 liters of 2% sodium hypochlorite for four and one-half hours; it was converted to the amide (m.p. 137–138°) through the acid chloride (13) in 95% yield. The amide was converted to the nitrile (b.p. 156–157°/15 mm.) in 86% yield by the method described for 4-cyanofluorene, and the nitrile was treated with phenylmagnesium bromide in the manner described, except that the mixture was refluxed for twelve hours. The ketimine hydrochloride was obtained as a yellow solid which was hydrolyzed to the ketone by warming with water for four hours. Recrystallization from petroleum ether (60–75°) gave prisms of the ketone; yield, 76%; m.p. 39.5–41° alone and when mixed with the ketone from (a).

Phenyl-(5,6,7,8-tetrahydro-2-naphthyl)carbinol. The carbinol prepared by reduction of 4.94 g. of 2-benzoyltetralin crystallized from 60–75° petroleum ether in fine colorless needles; yield, 3.44 g. (69%); m.p. 65.5–67°. It gives a bright orange-red color with concentrated sulfuric acid.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.7; H, 7.6.

Found: C, 85.2; H, 7.7.

1,1,1,2-Tetraphenyl-2-(5',6',7',8'-tetrahydro-2'-naphthyl)ethane (V). Phenyl-2-tetralylchloromethane was obtained as a liquid by passing dry hydrogen chloride into a solution of 7.79 g. of the carbinol in 50 cc. of benzene for two hours and then evaporating the solvent. The pentaarylethane prepared by interaction of 7.18 g. of the chloride and triphenylmethylsodium by the standard procedure crystallized when dissolved in petroleum ether. It was recrystallized by adding 100 cc. of petroleum ether to a solution of the ethane in 25 cc. of benzene; yield, 8.29 g. (65%); m.p. in air, 184–186°; in a vacuum, 186–186.5°.

Anal. Calc'd for $C_{16}H_{12}$: C, 93.1; H, 6.9.

Found: C, 92.8; H, 7.1.

1-Benzoylfluorene. A nearly quantitative yield of the amide was obtained from fluorene-1-carboxylic acid (14) through the acid chloride by the procedure described for the 4-isomer, and the amide was converted to the nitrile with phosphorus oxychloride and sodium chloride. The vacuum-distilled 1-cyanofluorene crystallized from alcohol in needles; yield, 46%; m.p. 94–94.5°.

Anal. Calc'd for $C_{14}H_9N$: N, 7.33. Found: N, 7.46; 7.59.

A mixture of 13.27 g. of 1-cyanofluorene, 100 cc. of benzene and the Grignard reagent from 11 cc. of bromobenzene in 130 cc. of ether was refluxed for six hours. After hydrolysis with cold ammonium chloride solution, addition of 200 cc. of 10% hydrochloric acid to the ether-benzene layer precipitated the ketimine hydrochloride as a gum which gradually crystallized. After being filtered and washed with acetone, the ketimine hydrochloride (16 g.) was heated with 180 cc. of water and 12 cc. of concentrated hydrochloric acid in a sealed tube at 180° for thirty-two hours. Extraction with ether removed the ketone from unhydrolyzed ketimine hydrochloride (5.5 g.). The 1-benzoylfluorene was obtained as platelets by sublimation; weight, 6.73 g.; m.p. 89–90°. A further 1.05 g. of the ketone was obtained by retreatment of the recovered ketimine hydrochloride.

Anal. Calc'd for $C_{20}H_{14}O$: C, 88.9; H, 5.2.

Found: C, 88.6; H, 5.1.

Phenyl-1-fluorylcarbinol. The carbinol obtained by reduction of 6.19 g. of 1-benzoylfluorene was recrystallized from 90–100° petroleum ether; yield, 4.53 g. (73%); m.p. 98–99°. It gives a deep green color with concentrated sulfuric acid.

Anal. Calc'd for $C_{20}H_{16}O$: C, 88.3; H, 5.9.

Found: C, 88.2; H, 6.0.

1,1,1,2-Tetraphenyl-2-(1'-fluoryl)ethane (VI). Phenyl-1-fluorylbromomethane, obtained from 3.13 g. of the carbinol and acetyl bromide, crystallized from 20 cc. of 90–100° petroleum ether (Norit) in fine, flat, colorless granules; yield, 3.04 g. (79%); m.p. 83–84°. It was shaken with 2.52 g. of triphenylchloromethane and 5 cc. of mercury in 50 cc. of benzene for forty-eight hours. The pentaarylethane was obtained as a fine colorless powder when triturated with a few drops of absolute alcohol and then 50 cc. of 60–75° petroleum ether; yield, 4.21 g. (91%); m.p. in air, 191–195°; in a vacuum, 201–203°.

Anal. Calc'd for $C_{39}H_{30}$: C, 94.0; H, 6.0.

Found: C, 93.9; H, 6.3.

Pentaphenylethane from triphenylchloromethane, diphenylbromomethane, and copper. Copper powder, prepared from 16 g. of hydrated copper sulfate and zinc powder (15), was washed well with acetone, dried, placed in a nitrogen-filled cylinder, and shaken with 2 g. of triphenylchloromethane and 1.77 g. of diphenylbromomethane in 35 cc. of benzene. After sixty hours of shaking, the filtered solution was evaporated and the residue triturated with petroleum ether; yield of pentaphenylethane, 2.29 g. (79%).

Rate measurements. These were carried out according to the procedure described by Bachmann and Osborn (2); methanol was used in place of ethanol in the *o*-dichlorobenzene, iodine, and pyridine mixture.

SUMMARY

The rates of dissociation of six new 1,1,1,2-tetraphenyl-2-arylethanes at 80° were determined and their half-life periods in the reaction with iodine were calculated. The six aryl groups, arranged in order of decreasing effectiveness on the rate of dissociation, were: 1-tetralyl, 1,2,3,4-tetrahydro-9-phenanthryl, 4-methyl-1-naphthyl, 4-fluoryl, 2-tetralyl, and 1-fluoryl.

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THE OXYNITRATION OF BENZENE TO 2,4-DINITROPHENOL¹W. E. BACHMANN, J. M. CHERMERDA,^{2a} N. C. DENO, AND E. C. HORNING^{2b}*Received December 31, 1947*

During World War II there was interest for a time in the preparation of picric acid by oxynitration of benzene. In this process, discovered by Wolfenstein and Boeters (1), benzene is converted into picric acid by the action of a hot solution of mercuric nitrate in nitric acid. The history and mechanism of the oxynitration reaction have been discussed in recent papers (2, 3).

Downing, Robertson, and Wright (4) developed a procedure for obtaining picric acid from benzene in one operation. The addition of benzene to a solution of mercuric nitrate in 50% nitric acid containing small amounts of aluminum and manganese ions at 65° was followed by a "boil-up" of the mixture at 115–120°. In the present study it was planned to work out conditions whereby 2,4-dinitrophenol could be prepared by oxynitration of benzene and then nitrated to picric acid by a nitrating agent more effective than the oxynitration mixture. A few runs indicated that the conversion of 2,4-dinitrophenol into picric acid by means of the oxynitration mixture was about 82% in contrast to the 96% conversion that could be effected with mixed acid. Wolfenstein and Boeters (1) had obtained 2,4-dinitrophenol by various procedures.

After considerable experimentation 72% yields of 2,4-dinitrophenol containing a few per cent of picric acid could be obtained based on the benzene that entered into the reaction. Benzene was added dropwise to a stirred solution of 10.65 molar nitric acid which was 0.37 molar with respect to mercuric nitrate; the temperature was kept constant at 50°. In Table I are shown the products obtained when the optimum conditions were employed; the yields are based on the benzene actually consumed and not on the amount added (about 7.5% of benzene escapes in the evolved gases).

It is seen that the by-products included nitrobenzene, *o*- and *p*-dinitrobenzene, and 2,4,2',4'-tetranitrodiphenylamine, in addition to carbon dioxide and oxalic acid. The presence of 2,4,2',4'-tetranitrodiphenylamine in the oxynitration mixture had not been reported previously.

¹ This investigation was carried out under contract OEMsr-245, recommended by the National Defense Research Committee, between the Regents of the University of Michigan and the Office of Scientific Research and Development in close collaboration with three other groups: Carmack, Baizer, Handrick, Kissinger, and Specht of the University of Pennsylvania; Westheimer, Segel, and Schramm of the University of Chicago; and Wright of the University of Toronto. The earlier work of the latter served as a useful guide in the investigation.

We are happy to acknowledge the aid of Dr. Ralph Connor who was Chief of the section in which this work was done and who suggested to us that 2,4-dinitrophenol rather than picric acid be prepared in the oxynitration reaction.

² Present address: (a) Merck and Company, Rahway, N. J.; (b) Department of Chemistry, University of Pennsylvania.

The effect of temperature, rate of benzene addition, and concentration of reagents on the yield and on the rate of 2,4-dinitrophenol formation were studied. The effect on the yield was determined by a batch procedure while the effect on the rate of the reaction was studied more conveniently by a continuous process.³

A temperature of 50° was found to be the optimum temperature for preparing 2,4-dinitrophenol by the oxynitration reaction by our procedure. At higher temperatures more of the 2,4-dinitrophenol was nitrated to picric acid with consequent lowering in yield, and more nitrobenzene was produced; thus, at 70° the combined yield of 2,4-dinitrophenol (16.9%) and picric acid (37.7%) was only 54.6% and the yield of nitrobenzene was 17–19%. At 40° the reaction was slower and the yield of 2,4-dinitrophenol was not increased.

The rate of addition of benzene is an important factor in determining the ratio of 2,4-dinitrophenol to nitrobenzene. If the benzene was added at such a rate that a liquid benzene phase was present in the stirred oxynitration mixture, considerable nitration of the benzene took place at the expense of the oxynitration

TABLE I
PRODUCTS OBTAINED BY OXYNITRATION OF BENZENE AT 50°

COMPOUND	YIELD, %
2,4-Dinitrophenol.....	68.4
Picric acid.....	4.0
Nitrobenzene.....	7.8
<i>o</i> -Dinitrobenzene.....	0.07
<i>p</i> -Dinitrobenzene.....	1.0
2,4,2',4'-Tetranitrodiphenylamine.....	0.05
Carbon dioxide.....	9.7
Oxalic acid.....	2.5

reaction. Thus, when all the benzene was added at the start of the experiment, the combined yield of 2,4-dinitrophenol and picric acid was 48.5% and the yield of nitrobenzene was 24.7%. As the addition time was increased, the yield of 2,4-dinitrophenol increased and that of nitrobenzene decreased until an optimum time was reached for the amounts and products recorded in Table I. However, no matter how long a time was taken for the addition of the benzene, a certain irreducible minimum of nitrobenzene was formed. This result suggested that some of the nitrobenzene is formed from an intermediate in the oxynitration reaction, probably nitrosobenzene, as suggested by Desvergnès (5).

Increasing the mercuric ion concentration markedly increased the rate of reaction (6), but had little effect on the yield of 2,4-dinitrophenol. Although aluminum ion has been employed by others in the oxynitration reaction, no beneficial effect was observed in the preparation of 2,4-dinitrophenol under the conditions of the present investigation. Although an increase in the concentra-

³ The details of these studies are too extensive to be included here. The descriptions of the procedures and the diagrams of the apparatus appear in OSRD report 4026.

tion of nitric acid markedly increased the rate of the reaction, it also favored the formation of nitrobenzene.

The chief function of manganese ion in the oxynitration reaction when it is employed is to catalyze the oxidation of the by-product oxalic acid by the nitric acid. This is of importance when the oxynitration solution is used repeatedly. If the oxalic acid is not destroyed, eventually a concentration is reached when solid mercuric oxalate precipitates; in the presence of sufficient manganous ion the concentration of the oxalic acid can be kept below the precipitation point and the oxynitration mixture can be used repeatedly provided the nitric acid concentration is maintained (conveniently by the addition of 98% nitric acid). The manganous ion also increases somewhat the rate of oxynitration and catalyzes the nitration of 2,4-dinitrophenol to picric acid.

It has been proposed (2, 3) that nitrosobenzene, benzenediazonium nitrate, and phenol are intermediates in the oxynitration reaction. In order to test this point we studied the behavior of these compounds in the oxynitration mixture under the same conditions employed for the oxynitration of benzene. The results are shown in Table II.

TABLE II
ACTION OF OXYNITRATION MIXTURE ON THREE INTERMEDIATES

COMPOUND	PRODUCTS; ^a YIELD, %			
	DNP	NB	DNB	Oxalic acid
Nitrosobenzene.....	67.9	6.6	1.3 ^b	3
Benzenediazonium nitrate	69.5	0	0	5
Phenol.....	71.3	0	0	6

* Abbreviations: DNP = 2,4-dinitrophenol; NB = nitrobenzene; DNB = crude dinitrobenzene.

^b The major portion of this fraction was 2,4,2',4'-tetranitrodiphenylamine.

In each of the three experiments the yield of 2,4-dinitrophenol⁴ (which was of high quality and contained only a little picric acid) was in the neighborhood of 70% and approached the yield obtained by oxynitration of benzene. The formation of nitrobenzene in 6.6% yield by oxynitration of nitrosobenzene is additional evidence that not all of the nitrobenzene formed in the oxynitration of benzene arises from direct nitration of benzene.

EXPERIMENTAL

Preparation of 2,4-dinitrophenol from benzene. A 1.5-liter three-necked flask was fitted with an Ace Trubore stirrer with a half-moon paddle. One neck was fitted with a condenser and the other with a long-stemmed dropping-funnel which dipped below the surface of the solution. Ground-glass connections were used throughout.

In the flask was placed 750 cc. of a solution 10.65 molar in nitric acid and 0.37 molar in mercuric nitrate prepared by adding 60 g. of mercuric oxide to 541 cc. of 70% nitric acid and

⁴ Carmack and co-workers obtained 2,4-dinitrophenol by the action of 50% nitric acid on benzenediazonium nitrate and on phenol and by the action of nitric oxide followed by nitric acid on nitrosobenzene.

diluting with water to 750 cc. About 0.1 g. of sodium nitrite was added to eliminate any induction period. To the stirred solution held at 50°, 50 g. of thiophene-free benzene was added at a continuous rate in the course of three and one-third hours. The mixture was stirred for an additional two and two-thirds hours at 50° and then chilled for twelve hours. The pale-tan colored precipitate of 2,4-dinitrophenol (containing less than 0.1% of picric acid) was filtered on a sintered-glass funnel and washed with two 50-cc. portions of 50% nitric acid and three 50-cc. portions of cold water; yield, 67 g.; m.p. 112–113°.

The filtrate and washings were extracted with three 100-cc. portions of benzene, and the combined benzene extracts were shaken with 30% aqueous triethanolamine (suggested by G. F. Wright). Acidification of the basic solution with concentrated hydrochloric acid precipitated a mixture of 7.5 g. of 2,4-dinitrophenol and 5.5 g. of picric acid. The total yields of all products are shown in Table I. The same results were obtained when the benzene was added in five 10-g. portions at sixty-minute intervals.

When the oxynitration liquor was used repeatedly, the nitric acid concentration was maintained by adding 18 cc. of 98% nitric acid after each 10 g. of benzene. The benzene (about 7.5%) that escaped with the evolved gases was determined by passing the gases through a Drechsel bottle containing 60 cc. of 98% nitric acid and 75 cc. of 95% sulfuric acid. The *m*-dinitrobenzene which was obtained by drowning the mixture in 750 cc. of ice and water and extracting with benzene was weighed.

Estimation of by-products. The oxalic acid which was formed was determined by adding calcium chloride to an aliquot of the oxynitration liquor, followed by addition of dilute aqueous ammonia. The calcium oxalate which precipitated was isolated and titrated in dilute sulfuric acid with standard potassium permanganate.

The carbon dioxide was determined by washing the evolved gases with ferrous sulfate solution, drying with calcium chloride and then absorbing the carbon dioxide in 40% potassium hydroxide solution.

The benzene solution remaining after the triethanolamine extraction was distilled. The fraction boiling at 190–210° was collected as nitrobenzene. Somewhat over 11 g. of the residues from several runs was steam distilled in order to remove nitrobenzene (5.51 g.), and the residual solid was subjected to fractional crystallization from benzene, chloroform, and ethanol with the aid of mechanical separation. In this manner there were obtained 0.37 g. of *o*-dinitrobenzene (0.26 g. with m.p. 116–117°), 5.02 g. of *p*-dinitrobenzene (4.58 g. with m.p. 171.5–174°) and 0.24 g. of 2,4,2',4'-tetranitrodiphenylamine (m.p. 201–203°).

The 2,4,2',4'-tetranitrodiphenylamine was identified by color tests (7), by its weakly acidic character (several extractions with 5% sodium hydroxide did not remove it completely from a benzene solution), by a mixed m.p. with an authentic specimen, by conversion of a sample to dipicrylamine, and by analysis.

Anal. Calc'd for $C_{12}H_7N_4O_8$: C, 41.3; H, 2.0; N, 20.1.

Found: C, 42.1; H, 2.4; N, 19.7.

Determination of picric acid. The method was based on the selective precipitation of nitron picrate from an aqueous acidic medium. Three grams of nitron reagent was dissolved in 25 cc. of 5% aqueous acetic acid and the filtered solution (after decolorization with Norit) was used immediately.

One-tenth gram of a 2,4-dinitrophenol-picric acid mixture was dissolved in 125 cc. of boiling water containing 2 cc. of aqueous sulfuric acid (prepared from 2 volumes of concentrated acid and 3 volumes of water), 5 cc. of the nitron solution was added, and the mixture was allowed to cool to room temperature in cold water for exactly one hour; if a longer time is allowed precipitation of brown nitron dinitrophenolate may occur. The yellow flocculent precipitate of nitron picrate was filtered on a weighed sintered-glass crucible, washed with 10–20 cc. of water, and dried at 75° for at least an hour. The weight of the precipitate multiplied by 0.4231 gave the weight of picric acid.

The method was checked with samples of known composition and with samples of dinitrophenol-picric acid mixtures from the oxynitration reaction to which additional picric acid had been added. Picric acid up to 20% in the mixtures could be determined to within 0.5%.

Nitration of 2,4-dinitrophenol to picric acid. A solution of 10 g. of 2,4-dinitrophenol in

25 cc. of warm concentrated sulfuric acid was cooled to 25° (partial crystallization set in) and 2.5 cc. of 98% nitric acid was added dropwise to the swirled mixture. The mixture was kept at room temperature for fifteen minutes and then at 65° for the same length of time. Drowning with 250 cc. of water yielded 11.96 g. (96.5%) of picric acid; m.p. 121–122.5° with previous sintering.

Effects of manganous ion in the oxynitration mixture. Oxalic acid is not appreciably oxidized by nitric acid (10.6 to 13 *M*) at the temperatures (45–60°) at which the oxynitration is generally carried out. In a liter of 10.65 *M* nitric acid and 0.37 *M* mercuric nitrate solution at 50° to which oxalic acid was added, 16 g. of oxalic acid remained in solution at equilibrium (after no more solid mercuric oxalate precipitated). The equilibrium point is reached slowly so that a greater concentration of oxalic acid may be reached for a time, but eventually the mercuric oxalate precipitates. If the manganous ion concentration in the oxynitration mixture is 0.67 *M*, the oxalic acid concentration rises to about 11.5 g. per liter but no further, and no mercuric oxalate precipitates. With this concentration of manganous ion in the oxynitration mixture, the products and yields were: 54.2% 2,4-dinitrophenol, 13.9% picric acid and 9.2% nitrobenzene.

The catalytic effect of manganous ion on the nitration of 2,4-dinitrophenol to picric acid was shown by the following experiments. When a suspension of 10 g. of 2,4-dinitrophenol in 50 cc. of 10.65 *M* nitric acid was kept at 50° for twenty-four hours with occasional swirling, the yield of picric acid was less than 2%. When the same mixture was 0.42 *M* with respect to manganous ion, a 32% yield of picric acid was obtained under the same conditions. This result explains the larger percentage of picric acid in the oxynitration product (see preceding paragraph) when manganous ion is present.

Conversion of nitrosobenzene, benzenediazonium nitrate, and phenol to 2,4-dinitrophenol by the oxynitration mixture. In three separate experiments 0.642 mole quantities (corresponding to 50 g. of benzene) of these three compounds were added to 750 cc. of a stirred solution 10.65 *M* in nitric acid and 0.37 *M* in mercuric nitrate over a period of two and one-half hours, and the mixture was stirred for an additional half hour; the temperature was kept at 50° and the nitric acid concentration was maintained by continuous addition of 98% nitric acid. The benzenediazonium nitrate and the phenol were added in the form of concentrated aqueous solutions. The reaction mixtures were worked up in the manner described for the oxynitration of benzene. The products are recorded in Table II.

SUMMARY

The preparation of 2,4-dinitrophenol by the oxynitration of benzene by a solution of mercuric nitrate in nitric acid is described.

The effects of various factors on the rate of the reaction and on the yield of 2,4-dinitrophenol are discussed.

Nitrosobenzene is oxynitrated to 2,4-dinitrophenol.

ANN ARBOR, MICHIGAN

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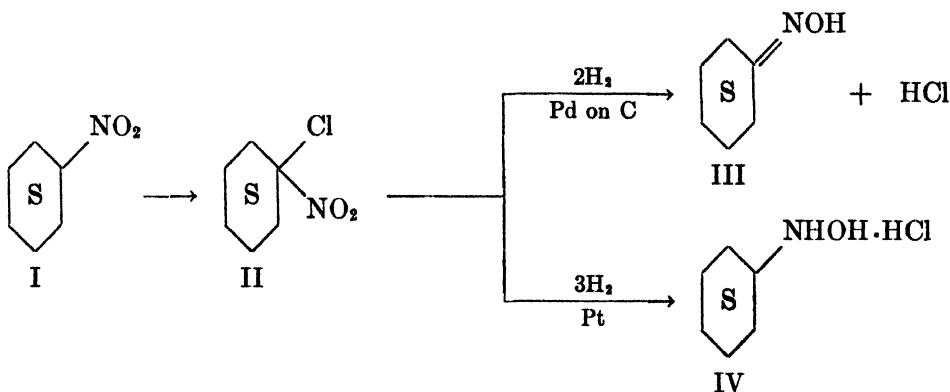
PREPARATION OF OXIMES AND N-ALKYLHYDROXYLAMINES BY HYDROGENATION OF α -CHLORO NITRO COMPOUNDS

J. A. ROBERTSON

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Various methods for the preparation of oximes and N-alkylhydroxylamines by partial reduction of aliphatic nitro compounds have been reported. For example, the potassium salt of aci-nitrocyclohexane has been treated with stannous chloride in hydrochloric acid to give an 80% yield of cyclohexanone oxime (1). Similarly, benzaldehyde oxime resulted from the reduction of the sodium salt of aci-phenylnitromethane with zinc or sodium amalgam (2). N-Alkylhydroxylamines have been the principal products obtained from the corresponding nitroparaffins by reduction with metals such as zinc (3) and tin (4), or with hydrogen in the presence of acid and a palladium catalyst (5). Other catalysts such as platinum (6) or nickel (7) have been used to hydrogenate nitroparaffins to amines and, according to a recent report, to oximes (8).

Recent work (9) has shown that nitro alkanes and nitro cycloalkanes can be converted to the corresponding oximes or N-alkylhydroxylamines by chlorination to α -chloro nitro alkanes and nitro cycloalkanes, and selective hydrogenation of these intermediates over specific catalysts.

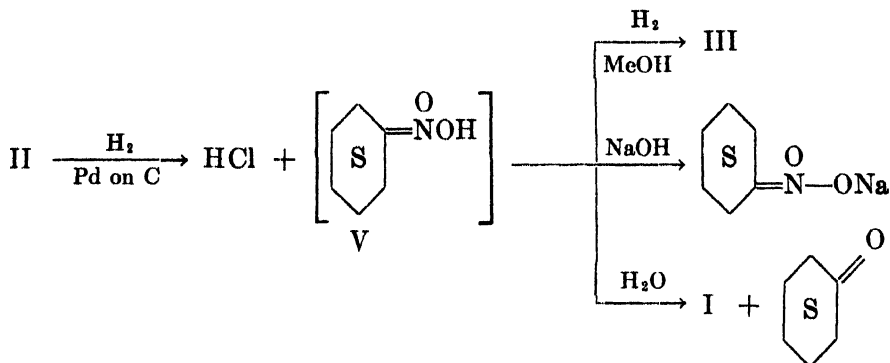


In experiments with 1-chloro-1-nitrocyclohexane (II), which was prepared according to a method (10) described for nitroparaffins by chlorination of the sodium salt of aci-nitrocyclohexane, hydrogenation in methanol over a palladium-on-charcoal catalyst produced up to 80% yields of cyclohexanone oxime (III). The exothermic reduction started at room temperature and proceeded under 10–50 pounds hydrogen pressure until two mole equivalents of the gas had been absorbed. Cyclohexanone oxime was isolated by evaporating the solvent after neutralizing the hydrochloric acid formed in the reaction. The minimum catalyst concentration and hydrogen pressure employed were interdependent variables. Thus, a high yield of product and a practical rate of hydro-

genation were achieved at 50 pounds or less hydrogen pressure only when at least 0.5% palladium based on 1-chloro-1-nitrocyclohexane was used, whereas 0.1% catalyst was sufficient to give equivalent results at 500 pounds hydrogen pressure.

When a platinum catalyst was substituted for palladium in the hydrogenation of 1-chloro-1-nitrocyclohexane, the reduction proceeded further to yield N-cyclohexylhydroxylamine hydrochloride (IV), which was converted to the free base with sodium hydroxide. N-Cyclohexylhydroxylamine was identified by the fact that it reduced Tollens' reagent, gave a neutral equivalent corresponding to the theoretical value, and was identical to a product obtained in an independent synthesis described previously (11).

In view of the fact that all previously reported reductions of nitroparaffins to oximes (1, 2) proceeded through the intermediate *aci* forms of the nitro compounds, it is postulated that the first step in the hydrogenation of 1-chloro-1-nitrocyclohexane involves removal of the halogen with the formation of *aci*-nitrocyclohexane (V). The extent to which further reduction proceeds to give different products depends on the selectivity of the catalyst used. It is not surprising that the reduction stopped at the oxime stage when palladium was employed, since it is known that oximes are not readily hydrogenated in the presence of acids with this catalyst (12).



The effect of various media on the course of the hydrogenation provided information on the mechanism of the reaction. Methanol and ethanol were suitable diluents for use in the hydrogenation of 1-chloro-1-nitrocyclohexane to cyclohexanone oxime, but when water was used the product consisted of a mixture of cyclohexanone and nitrocyclohexane. This is in agreement with the findings of previous investigators who reported that hydrogenation of α -chloro nitro alcohols over palladium catalysts in aqueous systems gave nitro alcohols (13) and hydroxycarbonyl compounds (14). The fact that no oximes were formed may be explained on the basis that, in the presence of aqueous acid, the intermediate *aci*-nitrocyclohexane hydrolyzed to the ketone and rearranged in part to the nitro compound.

Actual isolation of the proposed intermediate was achieved when a 75% yield of the sodium salt of *aci*-nitrocyclohexane was obtained from a hydrogenation

of the chloro nitro compound over palladium in a 10% aqueous sodium hydroxide solution. In this reaction the halogen was removed initially and the labile aci-nitrocyclohexane was converted to the stable sodium salt.

To illustrate the general applicability of this new synthesis, 2-chloro-2-nitropropane was hydrogenated over palladium-on-charcoal in a similar manner to give a 35% yield of acetone oxime.

EXPERIMENTAL

1-Chloro-1-nitrocyclohexane. 1-Chloro-1-nitrocyclohexane was prepared in substantially quantitative yield from the sodium salt of aci-nitrocyclohexane by reaction with chlorine in aqueous solution at -5 to 0° , according to a procedure described for other nitroparaffins by Henry (10). A distilled sample, b.p. $81-82^\circ/8$ mm., gave the following analyses:

Anal. Calc'd for $C_6H_{10}ClNO_2$: N, 8.6; Cl, 21.7.

Found: N, 8.6; Cl, 21.3.

Hydrogenation of 1-chloro-1-nitrocyclohexane. Except where otherwise designated, the following hydrogenations were carried out in a laboratory Burgess-Parr hydrogenation apparatus equipped with "Pyrex" brand glass pressure bottles. The hydrogenation vessel was charged with 0.1 mole of the compound to be reduced, 100 ml. of solvent, and the catalyst. The vessel was evacuated and then pressured with 40-50 pounds of hydrogen. The hydrogenations proceeded at room temperature with agitation, and the vessels were repressured with hydrogen when the pressure fell below 15 pounds. When absorption of hydrogen had ceased, the contents of the bottle were removed and the various products obtained were isolated as described below.

Palladium-on-charcoal.¹ In the experiment which gave the highest yield of cyclohexanone oxime, 16.35 g. (0.1 mole) of 1-chloro-1-nitrocyclohexane was hydrogenated over 1.6 g. of 10% palladium-on-charcoal in 100 ml. of methanol as described above. After 0.2 mole of hydrogen was absorbed the reaction stopped; the filtrate was neutralized with 10% aqueous sodium carbonate and most of the methanol was evaporated under reduced pressure, at which point cyclohexanone oxime precipitated. The yield was 9 g., (80%). The product melted at 88° . A similar result was obtained in a stainless-steel bomb at 500 pounds hydrogen pressure using 0.16 g. of 10% palladium-on-charcoal catalyst.

The above hydrogenation was repeated exactly except that 10% aqueous sodium hydroxide solution was substituted for the methanol. Only 0.1 mole of hydrogen was absorbed. The catalyst was removed from the resulting clear, aqueous solution as before. Evaporation of the solvent under reduced pressure deposited a white solid, which proved to be the sodium salt of aci-nitrocyclohexane. Acidification of an aqueous solution of this salt with hydrochloric acid resulted in the separation of an oil, which was extracted with ether and distilled. Nine grams of nitrocyclohexane, b.p. $95^\circ/22$ mm., was obtained. In a similar run where water was employed instead of caustic solution, a total of 10 g. of liquid was obtained, which consisted of a mixture of cyclohexanone and nitrocyclohexane, which were identified by their boiling points.

A 0.1-mole sample of 2-chloro-2-nitropropane was hydrogenated in methanol over palladium-on-charcoal as described above for 1-chloro-1-nitrocyclohexane. A 36% yield of acetone oxime (m.p. 58°) was isolated.

Platinum. Using a procedure similar to that described for the preparation of cyclohexanone oxime, 1-chloro-1-nitrocyclohexane was hydrogenated in ethanol in the presence of a platinum oxide catalyst. Following the absorption of 0.3 mole of hydrogen, the catalyst was removed and the solution was evaporated to dryness under reduced pressure. The

¹ This catalyst was purchased from Baker and Company, 113 Astor St., Newark, N. J., and consisted of 10% palladium supported on activated charcoal powder (Baker catalyst #25).

residual salt was recrystallized from ethyl acetate, was dissolved in water, and was made basic with 10% sodium hydroxide. The white, fluffy solid which precipitated was collected on a filter, dried, and was recrystallized from a 6:4 benzene-petroleum ether mixture. A 65% yield of N-cyclohexylhydroxylamine, m.p. 140° (11), was obtained. Neutral equivalent, calc'd 115; found 113. This compound reduced Tollens' reagent readily.

SUMMARY

1-Chloro-1-nitrocyclohexane has been hydrogenated to cyclohexanone oxime in high yield over a palladium-on-charcoal catalyst in nonaqueous systems. When a platinum catalyst was used, the reduction proceeded further to yield N-cyclohexylhydroxylamine hydrochloride.

Evidence is presented to show that the reaction proceeds through the intermediate aci-form of the nitro compound.

Acetone oxime was obtained from 2-chloro-2-nitropropane by hydrogenation over a palladium catalyst.

WILMINGTON, DEL.

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THE EFFECT OF pH ON THE STABILITY OF *CIS*-ACONITIC ACID IN DILUTE SOLUTION

J. A. AMBLER AND E. J. ROBERTS

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In the first description of *cis*-aconitic acid, Malachowski and Maslowski (1) noted that in aqueous solution it was rapidly converted by heat into the *trans*-acid. In a study of the electrical conductivity of dilute solutions of the two isomeric acids, Malachowski (2) found that the proportion of the *trans*-acid in equilibrated mixtures is approximately 85% and decreases slightly with elevation of the temperature and with dilution of the solution. Krebs and Eggleston (3) showed that in neutral solution sodium *cis*-aconitate is much more stable and that the most rapid and extensive conversion to the *trans*-isomer takes place in strongly acidic and strongly alkaline solutions. They point out, however, that the values they obtained are of uncertain accuracy because of interferences in the enzymic and chemical reactions used to determine *cis*-aconitic acid.

The strontium salt of *trans*-aconitic acid (4) is soluble when formed by double decomposition at room temperature, and precipitates only when the solutions are heated, but the strontium salt of *cis*-aconitic acid precipitates as the hexahydrate almost immediately on the addition of soluble strontium salts to cold solutions of soluble *cis*-aconitates, even in the presence of large excesses of *trans*-aconitates, as shown in Table I. This characteristic difference in precipitability of the strontium salts of the two acids has made possible a study of the stability of *cis*-aconitic acid and its alkali salts at pH values from 1 to 14 and at different temperatures.

The experiments recorded in Table II were undertaken to determine the range of stability of *cis*-aconitic acid in solutions of different pH values and temperatures, rather than the rate of the isomeric change. By precipitation from dilute solutions, strontium *cis*-aconitate hexahydrate has an apparent solubility equivalent to approximately 0.15% aconitic acid. Since 0.87% solutions were used this placed an upper limit of 80% on the determinable extent of the change to the *trans*-form, and made impossible the study of the equilibria reported by Malachowski (2). The high values of 23 to 33% isomerization of the *trans*-acid and salts reported by Krebs and Eggleston (3) would, however, lie within the range of the procedure described below, but when a like series of experiments was carried out with *trans*-aconitic acid no precipitates of strontium *cis*-aconitate could be detected. Attempts to study the isomeric change by determining aconitic acid as the mixed calcium-magnesium salt (5) and as the cadmium salt (4) proved unsuccessful because *cis*-aconitates largely inhibited the precipitation of the former and interfered in the precipitation of the latter.

From Table II it is evident that *cis*-aconitates are stable in neutral and slightly alkaline solutions, but unstable at high alkalinities, especially if the solutions

are heated. In acid solutions the stability decreases as the acidity increases. Only in highly acidic and highly alkaline solutions does temperature have a material effect on the amount of the *cis*-acid which disappears. In the pH range 2 to 6 there apparently is a progressive series of equilibria which are de-

TABLE I
PRECIPITATION OF STRONTIUM *cis*-ACONITATE IN PRESENCE OF *trans*-ACONITATE

ACONITIC ACIDS TAKEN		FOUND	RECOVERY
<i>trans</i>	<i>cis</i>	$\text{Sr}_2(\text{cis-C}_6\text{H}_7\text{O}_6)_2 \cdot 2\text{H}_2\text{O}$	<i>cis</i> - $\text{H}_3\text{C}_6\text{H}_5\text{O}_6$
<i>g./100 ml.</i>	<i>g./100 ml.</i>	<i>g./100 ml.</i>	%
3.5	0.0	0.0	0.0
3.0	0.5	0.608	66.0
2.5	1.0	1.536	83.4
2.0	1.5	2.435	88.1
1.5	2.0	3.310	89.9
1.0	2.5	4.139	89.9
0.5	3.0	5.034	91.1
0.0	3.5	5.835	91.0

TABLE II
EFFECT OF pH, TEMPERATURE AND TIME ON THE STABILITY OF *cis*-ACONITIC ACID
IN 0.05*M* SOLUTION

pH	<i>cis</i> -ACONITIC ACID RECOVERED AS STRONTIUM SALT									
	25°C.					65°C.			90°C.	
	0 Hrs.	24 Hrs.	48 Hrs.	72 Hrs.	96 Hrs.	24 Hrs.	48 Hrs.	72 Hrs.	4 Hrs.	
	%	%	%	%	%	%	%	%	%	
1	100.0	69.0	57.5	40.2	29.9	0.0	0.0	0.0	0.0	
2	100.0	79.3	75.9	57.6	48.3	24.1	27.6	24.1	28.7	
3	100.0	92.0	86.3	88.5	69.0	45.6	45.9	43.7	43.7	
4	100.0	98.8	94.3	94.3	83.9	59.8	63.6	63.6	59.8	
5	100.0	100.0	96.6	96.6	89.7	85.1	79.3	80.6	73.6	
6	100.0	100.0	98.8	98.8	94.3	98.8	98.0	97.7	92.0	
7	100.0	100.0	100.0	100.0	97.7	100.0	100.0	100.0	100.0	
8	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	
9	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	
10	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	98.8	
11	100.0	100.0	100.0	100.0	100.0	98.8	100.0	97.7	96.6	
12	100.0	100.0	98.9	98.8	96.6	94.3	92.0	86.4	89.7	
13	100.0	98.8	86.3		73.6	57.5	54.2	48.5	58.6	
14	100.0	92.0	45.0	0.0	0.0	0.0	0.0	0.0	0.0	

pendent on the pH of the solution. It appears that these solutions behave as mixtures of tri- or di-basic *cis*-aconitates with free *cis*-aconitic acid, and that the salts remain stable while the free acid undergoes the *cis* \rightleftharpoons *trans* isomerization. If this is so, the expected subsequent reaction *cis*-salt + *trans*-acid \rightleftharpoons *trans*-salt + *cis*-acid, whereby the same equilibrated mixture would result in all the acid

solutions, must be greatly inhibited, possibly because of non-dissociation of the molecules of either the salt or the acid, or the formation of complex anions containing undissociated metallic atoms such as are indicated by the work of Greenwald (6). Informative studies of these apparent equilibria are impossible until more precise methods of determining each of the isomeric aconitic acids in the presence of the other have been found.

EXPERIMENTAL

Strontium was determined by incinerating the salts and converting the ash to the sulfate. Aconitic acid was determined by the decarboxylation method of Roberts and Ambler (7).

Tristrontium cis-aconitate hexahydrate, $\text{Sr}_3(\text{cis-C}_6\text{H}_5\text{O}_6)_2 \cdot 6\text{H}_2\text{O}$. This salt precipitated almost immediately when an excess of a soluble strontium salt was added to a cold freshly prepared solution of *cis*-aconitic acid (8, 9) neutralized to pH 6.8 with potassium or sodium hydroxide. Precipitation was completed in a refrigerator. The salt was filtered from the cold solution, washed with ice-water and dried over calcium chloride. It forms small, spindle-shaped, colorless single crystals and aggregates of smaller crystals radiating from a common center. Yields: from 100 ml. of 3.5% *cis*-aconitic acid solution, 6.495 g. (91.1%); from 9 preparations, each from 100 ml. of 0.87% solution of *cis*-aconitic acid, average, 1.333 g. of strontium salt, the filtrates from which contained by analysis 0.153 ± 0.001 g. of aconitic acid.

Anal. Calc'd for $\text{Sr}_3(\text{C}_6\text{H}_5\text{O}_6)_2 \cdot 6\text{H}_2\text{O}$: Sr, 36.88; $\text{H}_2\text{C}_6\text{H}_5\text{O}_6$, 48.80.

Found: Sr, 36.90; $\text{H}_2\text{C}_6\text{H}_5\text{O}_6$, 48.87.

The salt lost water of hydration easily and came to constant weight when heated several hours at 140° , with loss of 4 molecules of water.

Anal. Calc'd for $4\text{H}_2\text{O}$: 10.01.

Lost at 140° : 9.56.

Heated at 140° ; Calc'd for $\text{Sr}_3(\text{C}_6\text{H}_5\text{O}_6)_2 \cdot 2\text{H}_2\text{O}$: Sr, 40.90; $\text{H}_2\text{C}_6\text{H}_5\text{O}_6$, 54.30.

Found: Sr, 40.80; $\text{H}_2\text{C}_6\text{H}_5\text{O}_6$, 54.25.

Tristrontium cis-aconitate trihydrate, $\text{Sr}_3(\text{cis-C}_6\text{H}_5\text{O}_6)_2 \cdot 3\text{H}_2\text{O}$. When solutions of potassium or sodium *cis*-aconitate prepared as above were heated to 95 – 100° and a soluble strontium salt was added, no immediate precipitation occurred, but on continued heating small colorless plates of tristrontium *cis*-aconitate trihydrate slowly deposited. Two preparations, each from 100 ml. of 0.87% solution of *cis*-aconitic acid, heated 3 hours in the steam-bath, gave yields of 1.222 and 1.235 g. of the salt. The salt slowly lost water of crystallization at 140° .

Anal. Calc'd for $\text{Sr}_3(\text{C}_6\text{H}_5\text{O}_6)_2 \cdot 3\text{H}_2\text{O}$: Sr, 39.90; $\text{H}_2\text{C}_6\text{H}_5\text{O}_6$, 53.82.

Found: Sr, 40.00; $\text{H}_2\text{C}_6\text{H}_5\text{O}_6$, 52.90.

Precipitation of strontium cis-aconitate in presence of trans-aconitate. Stock solutions of each of the isomeric potassium aconitates were prepared by dissolving 17.5 g. of pure *trans*-aconitic acid and 15.68 g. of *cis*-anhydroaconitic acid (8, 9, 10) in 400-ml. portions of water, neutralizing immediately with KOH solution to pH 6.8 and diluting to 500 ml. From the stock solutions, 100-ml. solutions containing a total of 3.5 g. of the isomeric acids in varying proportions were prepared. In each of these solutions 10.5 g. of strontium acetate hemihydrate was dissolved, and the solutions were allowed to stand in the refrigerator at about 0° overnight. The precipitates were collected in tared Gooch crucibles, washed with ice-water, dried at 140° overnight and weighed. The results are assembled in Table I.

When the weights of *cis*-aconitic acid in the 100-ml. solutions are plotted as abscissae against the corresponding weights of salt obtained as ordinates, a straight line results, the slope of which is slightly less than that of the line for complete precipitation, indicating a slight common ion effect of the excess of strontium ions at the lower concentrations. By extrapolation, the experimental line cuts the X-axis at approximately 0.15, indicating that solutions of *cis*-aconitic acid containing 0.15 g. or less per 100 ml. will produce no precipitate

of the strontium salt in mixtures with *trans*-aconitate. By comparing this value with that of 0.153 g. per 100 ml. found by analyses of filtrates from strontium *cis*-aconitate hexahydrate preparations, it is evident that the presence of a large excess of *trans*-aconitate has but an insignificant effect on the precipitation of strontium *cis*-aconitate hexahydrate.

Determination of stability of cis-aconitic acid in solutions of pH 1 to 14. Series of freshly prepared 100-ml. solutions containing 0.87 g. of *cis*-aconitic acid adjusted with HCl or KOH to each unit of pH from 1 to 14 inclusive were prepared and allowed to stand at 25° (room temperature), at 65°, and at 90° for different lengths of time. The solutions were then cooled to room temperature, and HCl or KOH solution was added as necessary to bring each solution to pH 6.8. The volume of each was adjusted to 100 ml., and 2.6 g. of strontium acetate hemihydrate was dissolved in each. After the solutions had stood at about 0° overnight, the precipitates of strontium *cis*-aconitate were collected in tared Gooch crucibles, washed with ice-water and dried at 140° to constant weight. From the precipitation line previously described the weights of *cis*-aconitic acid corresponding to the weights of strontium salt found were determined and calculated to per cent of acid taken. The results are given in Table II, in which, because of the solubility of the strontium salt, 0.0% recovery of *cis*-aconitic acid does not indicate 100% conversion to *trans*-aconitic acid.

The only non-volatile organic acid which could be found in the filtrates was aconitic acid. Decarboxylation in solutions of like composition and pH of 2, 3, and 4 heated for 4 hours at 90° (11, 12) amounted to but 0.07%, 0.13%, and 0.66%, respectively, of the aconitic acid present, as determined by loss of acidity. Since solutions of aconitic acid are most actively decarboxylated at pH 2 to 4 (11), no determinations of extent of decarboxylation were made on solutions of higher or lower pH.

SUMMARY

Tristrontium *cis*-aconitate tri- and hexa-hydrates have been prepared. The hexahydrate precipitates almost immediately from cold solutions, and the presence of large excesses of soluble *trans*-aconitates has no significant effect on its precipitation. It has been used to demonstrate that, in dilute solutions at pH 7 to 10, *cis*-aconitates are stable at temperatures up to 90°. Isomerization to *trans*-aconitates takes place at lower and higher pH values. Only in highly alkaline solutions does increase in temperature cause extensive increase in the amount of *cis*-aconitic acid or aconitate transformed.

NEW ORLEANS, LA.

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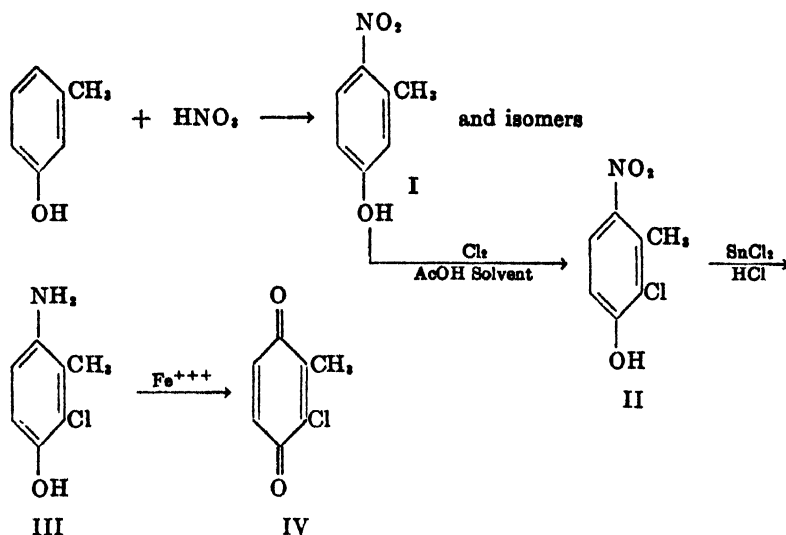
PREPARATION OF THE CHLOROTOLUQUINONES

JAMES CASON, CHARLES F. ALLEN, AND SIDNEY GOODWIN

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In order to make a study, to be reported later, of the addition of halogen acid to halotoluquinones, it was necessary to prepare a quantity of the three chlorotoluquinones. Two of these, the 5-chloro- and 6-chloro- isomers, have previously been obtained by several methods and their preparation offered no difficulty. 5-Chlorotoluquinone (1-4) was obtained by addition of hydrogen chloride to toluquinone and oxidation of the resultant 5-chlorotoluhydroquinone, in an over-all yield of 69%. 6-Chlorotoluquinone (5-9) was obtained by dichlorination of *o*-cresol and oxidation of the 4,6-dichloro-*o*-cresol, in an over-all yield of 42%.

3-Chlorotoluquinone (IV) has been prepared only by Raiford (3), according to the illustrated sequence of reactions beginning with *m*-cresol.



It seems surprising that chlorine should preferentially enter the 2-position in 4-nitro-*m*-cresol (I), and Kehrman and Tichvinsky (10), who assumed that chlorine enters the 6-position, reported a series of compounds from this reaction different from those obtained by Raiford. In a later paper (11), Raiford investigated the chlorination products more carefully, and again obtained as principal product the isomer, II, but obtained from the mother liquors a very small amount of an isomeric chloronitro-*m*-cresol, which was shown to be the 6-chloro- isomer by conversion to 5-chlorotoluquinone. Since this isomer gave an aminophenol whose diacetate had a melting point in agreement with that reported by Kehrman and Tichvinsky, it was concluded that these workers obtained the 6-chloro- isomer because they did not purify the chlorination prod-

uct, but reduced the crude mixture and acetylated the crude amine. In repeating these reactions, we have confirmed Raiford's work in essentially all respects, and have obtained 3-chlorotoluquinone by the indicated sequence of reactions. After isolating the isomer, II, from the chlorination products of I, we reduced the material from the combined mother liquors, acetylated the crude aminophenol, and attempted to isolate the isomeric diacetate reported by Kehrmann and Tichvinsky; however, repeated crystallization failed to yield a pure sample of the diacetyl derivative reported by these workers.

Raiford (3) reported 38–40% yield of I from the nitration of *m*-cresol with concentrated nitric acid in acetic acid according to Staedel and Kolb (12). The latter workers reported 33% average yield, but mentioned that in some runs the steam-distillation residue was a black amorphous mass from which the isomer, I, was obtained in poor yield. All our runs were of this latter variety, and the nitro compound, I, was most conveniently obtained, although in only 18% yield, by nitration of *m*-cresol with dilute nitric acid. The yield of 2-chloro-4-nitro-*m*-cresol, II, was not reported by Raiford, but our yield of pure product did not exceed 25% although the yield of crude product was about 76%. Thus, these reactions do not constitute a convenient approach to 3-chlorotoluquinone in quantity, in spite of the fact that the over-all yield in the last two steps is 87%.

The commercially available 6-chloro-2-nitrotoluene would appear to be a convenient starting point for preparation of the quinone, IV; however, a consideration of the literature reveals that no high-yield method has been developed for conversion of a nitro compound to the corresponding *p*-benzoquinone. Excellent yields may usually be obtained from a phenol by the coupling, reduction, and oxidation route (13), but conversion of an amine to a phenol is frequently unsatisfactory. For example, Smith and Opie (14) were able to obtain no better than 55% yield of 2,3-dimethylphenol from the amine even after considerable study of the conversion and use of a rather tedious process. Direct oxidation of 2-methyl-3-chloroaniline by three procedures gave us yields of 6.5–14% of the quinone. An effort was made to introduce a favorable *p*-substituent by way of acetylation, nitration, hydrolysis, and reduction; however, oxidation of the product gave no *p*-quinone at all. This observation is consistent with the findings of Morgan and Glover (15), who isolated the 6-nitro derivative from nitration of 2-methyl-3-chloroacetanilide. These workers obtained the 4-nitro derivative by nitration of the benzenesulfonamide, but this route does not seem attractive.

In view of these results, the electrolytic reduction of 6-chloro-2-nitrotoluene to the corresponding aminophenol was considered. Raiford (3) has prepared 2-methyl-4-amino-5-chlorophenol in unspecified yield by electrolytic reduction of 3-nitro-4-chlorotoluene, and he obtained 5-chlorotoluquinone by oxidation of this aminophenol. Gattermann (16) had earlier obtained 5-bromotoluquinone from aminophenols prepared by electrolytic reduction. These appear to be the only examples of such a route for quinone synthesis; however, electrolytic reduction of nitrobenzene to *p*-aminophenol has been studied extensively,

the report of Brigham and Lukens (17) being especially useful. Following the general procedure developed by these authors, but using for the reduction a standard perforated cylindrical platinum cathode, and oxidizing the diluted reduction mixture without isolating the aminophenol, no 3-chlorotoluquinone could be obtained. Further study of the reaction has shown that in this instance it is necessary to increase the sulfuric acid concentration in the catholyte to 75%, and it has been possible to define conditions under which over-all yields of quinone in the range 67–78% may be obtained. In all runs, no effort was made to isolate the aminophenol. The catholyte was simply diluted and oxidized. It is of interest that although the aminophenol, III, prepared *via* the nitrophenol as shown in the chart, is oxidized in nearly quantitative yield by ferric ion, the same compound prepared by electrolytic reduction is oxidized by ferric ion in considerably lower yield than obtained by dichromate oxidation. It is probable that this lowered yield is caused by an impurity which catalyzes decomposition of the quinone during the steam distillation used with the ferric ion oxidation. When dichromate oxidation was used the quinone was extracted with ether and a quantity of tarry material was removed by filtration before the extract was steam distilled. When this tarry material was included in the steam distillation the yield of quinone was lowered about 10%.

Since this method for preparing 3-chlorotoluquinone is simple, efficient, and rapid, and a wide variety of aromatic nitro compounds is available, the generality of the method for preparation of other *p*-benzoquinones is being studied.

EXPERIMENTAL

5-Chlorotoluquinone.¹ A mixture of 16.8 g. of pulverized, freshly steam-distilled toluquinone and 12 ml. of 18% aqueous hydrochloric acid was worked into a paste, then 30 ml. of concentrated hydrochloric acid was added dropwise with mixing during about fifteen minutes. The mixture became purple-black (quinhydrone) during this operation and warmed slightly. After standing for two hours at room temperature the reaction was completed by warming on the steam-bath for about twenty-five minutes, the mixture becoming light gray. The hydroquinone was collected by suction filtration, washed with a little water, then transferred to a flask containing 390 g. of ferric sulfate nonahydrate, 600 ml. of water, and 24 ml. of concentrated sulfuric acid. This mixture was indirectly steam-distilled immediately. From the distillate was obtained 13.0 g. of quinone by filtration and 1.8 g. additional by ether-extraction of the aqueous filtrate. Total yield, 14.8 g. (69%), m.p. 92–97°. One crystallization from hexane gave bright yellow needles melting at 102.8–103.9°. When there was used for this preparation a sample of toluquinone which had darkened from long storage, no chlorotoluquinone could be isolated.

6-Chlorotoluquinone. A solution of 108 g. (1 mole) of commercial *o*-cresol in 600 ml. of glacial acetic acid was treated with 2 moles of chlorine generated from potassium permanganate and hydrochloric acid. After addition was complete the mixture was diluted with a large volume of cold water, and the precipitated dichloro-*o*-cresol was collected and washed with water. The moist product was dissolved by heating in 1.5 liters of 70% acetic acid, and while the temperature was kept at approximately 70° by cooling, 110 g. of chromic anhydride was added slowly with swirling of the mixture. After addition was

¹ Several authors have reported the addition of halogen acid to quinones; however, few details are given. The procedure described here is based primarily on that used by Kehrman, Silva, and Keleti (18) for preparation of dihaloquinones.

complete the mixture was allowed to stand about one-half hour, then diluted with ice and water. The precipitated 6-chlorotoluquinone was collected by suction filtration, washed, and dried; wt. 95 g. (61%). This crude product was steam-distilled, about 1.5 liters of water being required. The quinone from the distillate was crystallized from 50% aqueous alcohol to yield 65 g. (42%) of yellow prisms, m.p. 88.4–89.9°. The best sample obtained by further crystallization melted at 89.9–90.2°.

4-Nitro-m-cresol (I). To a mixture of 84 ml. of concentrated nitric acid and 300 ml. of water there was added with swirling 70 g. of technical *m*-cresol, the temperature being maintained at 20–25° by cooling. After the mixture had stood an additional hour at the same temperature, with frequent shaking, the dark oily layer was separated and steam distilled until the distillate ran clear. The residual tar was extracted four times with 200-ml. portions of boiling water, the extracts being carefully decanted from the tar. After the total extracts had been filtered through Supercel, 40 ml. of 12 *N* sodium hydroxide and 40 g. of sodium chloride were added, and the mixture was concentrated to about 200 ml. The salt crystallizing on cooling was washed with small portions of alcohol and ether and combined with a small second crop of salt obtained by concentrating the filtrate. A solution of the salt in 300 ml. of water was acidified with 20 ml. of concentrated hydrochloric acid and treated with charcoal. The 4-nitro-*m*-cresol which crystallized on cooling weighed 18.0 g. (18%), m.p. 125–126°. One crystallization from water yielded material melting at 128–129° [literature (3, 12), 127–129°].

2-Chloro-4-nitro-m-cresol (II). The chlorine generated from 2.18 g. of potassium permanganate and 15 ml. of concentrated hydrochloric acid (calc'd wt. of chlorine, 2.44 g., 0.034 mole) was passed into a solution of 5 g. (0.033 mole) of I in 30 ml. of glacial acetic acid, during about 15 minutes. The reaction mixture warmed slightly. After standing one and one-half hour, the reaction mixture was diluted with 180 ml. of water and allowed to stand overnight. The precipitate was collected, washed with water, dried, and systematically crystallized from benzene. From 4.6 g. of crude product, the total yield of the isomer, II, consisting of short white needles, was 1.5 g. (25%), m.p. 132.5–134°. The best sample melted at 133.5–134.6° [Raiford (3) reported m.p. 133°].

2-Chloro-4-amino-m-cresol (III) was prepared by reduction of 0.7 g. of the nitro compound, II, dissolved in 1 ml. of ethanol, with 3.4 g. of stannous chloride dihydrate in 3.5 ml. of concentrated hydrochloric acid. After adding an additional 6 cc. of concentrated hydrochloric acid and cooling, the precipitated salt was collected and dissolved in hot water. On neutralization of the filtered solution with solid ammonium carbonate, the aminophenol, III, precipitated. After solution in hot ethanol, filtration, and precipitation by addition of water, the product melted at 162–166° (dec.). For a recrystallized sample, Raiford (3) reported m.p. 166–167°. On acetylation with 2.1 equivs. of acetic anhydride in presence of a trace of sodium acetate, the *diacetyl derivative of III* was obtained. After crystallization from benzene, the m.p. was 177–180° [literature (3), m.p. 178°].

3-Chlorotoluquinone (IV). From *2-chloro-4-nitro-m-cresol*. The nitro compound, II, (1.0 g.) was reduced as described above, and the reaction mixture was diluted with 50 ml. of water. After addition of 40.5 g. of ferric sulfate nonahydrate the mixture was steam-distilled at once. From the distillate there was removed 0.55 g. of quinone by filtration, m.p. 52.5–54.1°, and 0.15 g. of quinone by ether extraction of the aqueous filtrate, m.p. 52.4–53.8°; total yield, 87%. The best sample of quinone crystallized from hexane as yellow needles, m.p. 54.0–55.5° [Raiford (3) reported 55°].

From 6-chloro-2-nitrotoluene. Conditions giving the best results are described in detail, while results obtained under other conditions but using the same equipment are included in Table I. Better yields are obtained at lower current densities, where the hydrogen over-voltage is lower. Although Brigham and Lukens (17) report that a copper cathode may be used for the reduction of nitrobenzene to *p*-aminophenol, we were able to obtain no quinone at all from 6-chloro-2-nitrotoluene under a variety of conditions, using for the reduction a copper cathode of the excellent design described by Lukens (19). It is possible that the hydrogen over-voltage for copper is too high for reduction of this nitro compound to a

hydroxylamine, so that products resulting from further reduction are obtained; however, it has been claimed that copper has a catalytic effect in this reduction. Since a platinum cathode was found to be satisfactory this matter was not pursued further, and such factors as the purity of the copper were not investigated.

All reductions were carried out in a two-compartment cell, the inner compartment, containing the catholyte, consisting of a dense alundum extraction thimble, 4.5 x 11 cm. This was placed in a 250-ml. beaker containing the anolyte. The cylindrical anode (7.5 cm. high and 6 cm. in diameter) was of $\frac{1}{4}$ -inch sheet lead, and the anolyte was 75% sulfuric

TABLE I
PREPARATION OF 3-CHLOROTOLUQUINONE

CURRENT DENSITY (AMPS./SQ. DEC.)	EQUIVS. OF CURRENT	CONC. OF H ₂ SO ₄ , %	OXIDIZING AGENT	YIELD, %
1.65	1.0	50	Fe ⁺⁺⁺	0 ^a
1.65	2.7	92	Fe ⁺⁺⁺	13 ^b
1.65	2.0	75	Fe ⁺⁺⁺ Dichromate	32 ^c 54.5 ^c
1.0	1.5	75	Dichromate	67 ^d 62.5 ^d
1.0	1.1	75	Dichromate	63
0.6	1.1	75	Dichromate	67 ^e 58.5 ^e

^a At the end of the reduction the catholyte contained sulfur, sulfur dioxide, and some unreduced nitro compound. In none of the other runs in this table was unreduced nitro compound recovered.

^b This procedure is similar to that used by Raiford (3) and Gattermann (16).

^c The catholyte was divided into two equal portions, and each oxidized as indicated. In other runs, similarly higher yields were obtained with dichromate.

^d The catholyte was divided into two equal portions which were oxidized in the same way, except that one was worked up after two hours, the other after standing overnight. The portion worked up after two hours gave the lower yield of a product which had a lower melting point. All other dichromate oxidations were allowed to stand overnight.

^e The catholyte was divided into two equal portions which were oxidized in the same manner, but in one the tar was not filtered from the ether extract before steam-distillation of the product and the lower yield was thus obtained. This difference in yield was again observed when two separate runs were worked up in these ways.

acid. The level of acid in the anolyte and catholyte compartments should be the same. The cylindrical cathode was of platinum, 5.3 cm. high and 2.8 cm. in diameter, perforated with about 1,700 holes of 1.0 mm. diameter. The area of the holes was ignored in calculating current density; a cathode area of 0.5 sq. dec. was assumed. The mixture in the cathode compartment was 80 ml. (± 4 ml.) of 75% sulfuric acid and 10.0 g. (0.058 mole) of commercial 6-chloro-2-nitrotoluene.

During a reduction, a propeller-type glass stirrer with two blades, mechanically driven at sufficiently high speed to keep the nitro compound finely dispersed, was placed inside the cathode, and the cell was kept at a temperature of 50-70°. Heating was necessary in order to increase the solubility of the nitro compound (m.p. 35-40°) and to prevent clogging of

the electrode with solids; however, an elevated temperature has been reported as also improving reduction efficiency. For reduction, a current of 0.3 amp., requiring a potential at the electrodes of 2.5 volts, was passed for 22.9 hours, thus delivering 6.87 amp. hrs. at a current density at the cathode of 0.6 amp./sq. dec. Since the reduction of each molecule of nitro compound requires four electrons, the current used supplies 1.1 times the theoretical equivalency of electrons.

At the end of the reduction the catholyte was nearly black but clear and free of tar or other solid matter. It was diluted with water to a volume of 500 ml., then cooled in an ice-bath while there was added with swirling a solution of 9 g. (0.03 mole) of sodium dichromate dihydrate in 10 ml. of water, during about five minutes. After the mixture had stood overnight at room temperature the precipitate of quinone and tar was collected by suction filtration. Both the aqueous filtrate and tar were extracted with ether several times until the extracts became nearly colorless. The ether extracts were steam distilled, about 200 ml. of water being required, and the quinone was extracted from the distillate with ether. Removal of ether on the steam-bath left a residue of quinone weighing 6.1–7.1 g. (67–78%). On cooling, the quinone crystallized as yellow needles, m.p. 52–55.8°. A sample weighing 7.1 g. was crystallized from hexane to yield 6.7 g. of quinone melting at 54.9–55.8°.

As is evident from the data in Table I, nearly the same results were obtained when the reduction was carried out at a current density of 1 amp./sq. dec., but increasing the current density beyond this point lowers the yield appreciably.

SUMMARY

Details are reported for the preparation of the three chlorotoluquinones. Raiford's work on the chlorination of 4-nitro-*m*-cresol to give 2-chloro-4-nitro-*m*-cresol has been corroborated in all details.

A high-yield method has been developed for synthesis of 3-chlorotoluquinone from 6-chloro-2-nitrotoluene, proceeding by way of electrolytic reduction to the corresponding *p*-aminophenol and oxidation of this intermediate to the quinone.

BERKELEY, CALIFORNIA

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THE ACYLATION OF FURAN AND THIOPHENE WITH ALIPHATIC ANHYDRIDES IN THE PRESENCE OF BORON TRIFLUORIDE-ETHERATE¹

JOHN V. HEID AND ROBERT LEVINE

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In connection with a research program in progress in this laboratory on the use of boron trifluoride in organic syntheses, it was of interest to investigate the acylation of furan and thiophene with anhydrides using the etherate to effect the condensations.

Although our work is not fully completed, it seemed desirable to publish an account of the progress we have made to date, since other workers have used gaseous boron trifluoride or its complexes for certain similar reactions.

Meerwein and Vossen (1) have reported the acylation of benzene and other aromatic compounds with anhydride using gaseous boron trifluoride as the condensing agent. Given and Hammick (2) have acylated thiophene with benzoic anhydride. By saturating a solution of the anhydride and thiophene with gaseous boron trifluoride, these workers obtained a 40% yield of 2-benzoylthiophene. More recently, Hartough and Kosak (3) have shown that when catalytic amounts of a complex of ortho-phosphoric acid and boron trifluoride [$(\text{H}_3\text{PO}_4)_3 \cdot \text{BF}_3$] are allowed to react with thiophene and acetic anhydride, a 63% yield of 2-acetylthiophene is obtained. Earlier, these workers found that catalytic amounts of iodine (4), hydriodic acid (5), and anhydrous zinc chloride (5) also cause anhydrides to condense with thiophene and furan in high yields.

In the present investigation we have found that a catalytic amount of boron trifluoride-etherate effects the condensations of thiophene and furan with acetic, propionic, and *n*-butyric anhydrides in high yields. In order to determine the best conditions for carrying out these reactions, a detailed study was made of the acylation of furan with acetic anhydride. These experiments are summarized in Table I. It can be seen that fourteen grams of the complex added rapidly to 1.0 mole of furan and 1.15 moles of acetic anhydride gave the highest yields of 2-acetylfuran. It is of interest to note that when the above quantities of reactants were used and the reaction mixture allowed to stand overnight before being hydrolyzed the yield of the ketone was decreased to 54%. The yields of the 2-acylthiophenes and the 2-acylfurans which have been prepared are given in Table II.

In order to explain how a catalytic amount of boron trifluoride-etherate effects these condensations, we suggest the following possible mechanism for these reactions. The acylation of furan with acetic anhydride is taken as an example.

¹ This work is based on a thesis to be submitted by John V. Heid in partial fulfillment of the requirements of the degree of Master of Science at the University of Pittsburgh.

The furan used in this investigation was contributed by E. J. du Pont de Nemours and Co., Inc.

EXPERIMENTAL

The 2-acylfurans. (a) *2-Acetylfuran.* The apparatus used in these experiments consisted of a 500-ml. three-necked round-bottomed flask equipped with a mercury-sealed stirrer, a reflux condenser (protected by Drierite), and a cork carrying a thermometer so that the temperature of the reaction mixture could be recorded. One mole (68 g.) of furan and 1.15 moles (123 g.) of 95% acetic anhydride were placed in the flask. The reaction mixture was cooled to 0° in an ice-bath. To the rapidly stirred reaction mixture, 14 g. of redis-

TABLE I
YIELDS OF 2-ACETYLFURAN FROM ONE MOLE OF FURAN UNDER VARIOUS
EXPERIMENTAL CONDITIONS

MOLES OF ACETIC ANHYDRIDE	GRAMS OF $\text{BF}_3 \cdot (\text{C}_2\text{H}_5)_2\text{O}$	RATE OF ADDITION OF CATALYST	YIELD, %
1	3.5	rapid ^a	44
1	3.5	rapid ^a	51
1.15	3.5	rapid ^a	56
1.15	6.9	slow ^b	54
1.15	11.5	slow ^b	54
1.15	14	rapid ^a	77

^a Added all at once.

^b Added over a period of one hour.

TABLE II
YIELDS OF 2-ACYLFURANS AND 2-ACYLTHIOPHENES

PRODUCT	B.P.		YIELD, %
	°C	mm.	
2-Acetylfuran	45-48	5	77
2-Propionylfuran	61-63	6	81
2- <i>n</i> -Butyrylfuran	76-78	7	93
2-Acetylthiophene	80-81	7	73
2-Propionylthiophene	88-89	6	79
2- <i>n</i> -Butyrylthiophene	96	4	89

tilled boron trifluoride-etherate^a was added rapidly (all at once). The temperature of the reaction mixture rose to 110°, then quickly dropped to 0°. The ice-bath was removed and the contents of the flask allowed to come to room temperature. Stirring was continued for one-half hour longer, and about 200 ml. of water was added to hydrolyze the reaction mixture. The phases were separated and the aqueous phase was extracted several times with chloroform. The organic phases were separated again and the chloroform solution of the 2-acetylfuran was dried over Drierite. The chloroform was distilled at atmospheric pressure and the residue fractionated *in vacuo* through a Spitz-Vigreux flask. In this way 85 g.

^a The boron trifluoride-etherate used in this investigation was purchased from General Chemical Company, New York, N. Y.

(77%) of 2-acetylfuran, b.p. 45–48° at 5 mm., was obtained. Its semicarbazone melted at 149–150° corr. (6).

(b) *2-Propionylfuran*. The procedure followed was the same as that for 2-acetylfuran with the following changes. Propionic anhydride (150 g., 1.15 moles) was used. Upon addition of the catalyst, the temperature rose to 65° and dropped to 0° more slowly. In this experiment, 100 g. (81%) of 2-propionylfuran, b.p. 61–63° at 6 mm., was obtained. Its semicarbazone melted at 186–187° corr. (6).

(c) *2-n-Butyrylfuran*. The above procedure was used with the following changes. *n*-Butyric anhydride (182 g., 1.15 moles) was used. Upon addition of the catalyst, the temperature of the reaction mixture rose to 40° and dropped to 15° slowly. In this experiment 128 g. (93%) of 2-*n*-butyrylfuran, b.p. 76–78° at 7 mm., was obtained. Its semicarbazone melted at 190–191° corr. (6).

The 2-acylthiophenes. (a) *2-Acetylthiophene*. The procedure used was similar to that used with the furan compounds with the following changes. Thiophene (84 g., 1.0 mole) was used and the reaction mixture was not cooled in an ice-bath before the catalyst was added. Rapid addition of the catalyst caused the temperature of the reaction mixture to rise to 30°. The reaction mixture was rapidly heated to 110° and then the temperature was allowed to drop to room temperature. In this experiment there was obtained 92.5 g. (73%) of 2-acetylthiophene, b.p. 80–81° at 7 mm. Its semicarbazone melted at 190–191° (7).

(b) *2-Propionylthiophene*. The procedure was the same as that with 2-acetylthiophene with the following changes. Propionic anhydride (1.15 moles, 140 g.) was used. Upon the addition of the catalyst the temperature of the reaction mixture rose to 70°, then slowly dropped to 45°. The reaction mixture was heated to 110° and then allowed to come to room temperature. The ketone was isolated in the regular fashion. In this experiment there was obtained 110 g. (79%) of 2-propionylthiophene, b.p. 88–89° at 6 mm. Its semicarbazone melted at 172.5–173.5° corr. Steinkopf and Schubart (8) reported the melting point as 167°. We prepared a sample of 2-propionylthiophene by their method and found that the melting point of its semicarbazone was 172.5–173.5° corr. A mixed melting point of this semicarbazone with ours showed no depression.

(c) *2-n-Butyrylthiophene*. The procedure followed was the same as that given above with the following changes. *n*-Butyric anhydride (182 g., 1.15 mole) was used. Upon the addition of the catalyst the temperature rose to 70° and then dropped to 60°. The reaction mixture was then heated to 110° and allowed to cool to room temperature. In this experiment, there was obtained 137 g. (89%) of 2-*n*-butyrylthiophene, b.p. 96° at 4 mm. Its semicarbazone melted at 177° corr. (8).

SUMMARY

Furan and thiophene have been acylated with acetic, propionic, and *n*-butyric anhydrides in high yields using catalytic amounts of boron trifluoride-etherate as the condensing agent.

A possible mechanism for the reaction has been presented.

PITTSBURGH 13, Pa.

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nucleus being substituted by a chain of four carbon atoms, and containing a 2-propylamino "side chain."

It was considered desirable to make a study of the effect of substitution on this molecule on its analeptic and pressor activities.

In 1944, after this work was completed, Rohrmann and Shonle (8) reported on the pressor activity of a number of aliphatic amines. They found that maximum activity could be associated with a seven or eight atom carbon chain with the amino group in the C-2 position.

In the present study, the amino alcohols were prepared by two methods: (a) the reduction of the corresponding nitro alcohol with iron and hydrochloric acid, and (b) the high pressure catalytic hydrogenation over Raney nickel of the oxime and methylimine of the corresponding keto alcohol. Procedure (a) proved to be satisfactory in that it gave the desired product in reasonable yield. Procedure (b) gave a relatively large yield of what seemed, at first, to be the desired product. The compound was a colorless, amine-odored liquid that distilled at a temperature that was close to what was expected. However, the neutral equivalent was abnormally high. Rectification on a spiral column having fifteen theoretical plates gave no improvement. Hence, the impurity must either have nearly the same boiling point as the amino alcohol or else distill with it as a binary azeotrope. The corresponding diol could fit well into either category and its presence could be explained by hydrolysis of the oxime during hydrogenation followed by reduction of the resultant keto alcohol. This hypothesis was given added weight by the fact that if a small quantity of added keto alcohol was hydrogenated with the oxime, the rectified amino alcohol gave an even higher neutral equivalent. Attempts at purification involving the preparation of the hydrochloride, hydrobromide, sulfate, picrate and carbamate failed. The hydrobromide alone precipitated from dry ether, and then only as an oily solid between -70° and -50° . An attempt at disproportionation between an acidified aqueous solution and diethyl ether likewise proved unsuccessful. Steam distillation failed due to severe foaming. The problem was solved by the passage of hexane vapors through an acidified aqueous solution of the amine. Notwithstanding the fact that the process was run at $30-40^{\circ}$, by the employment of reduced pressure, a considerable amount of decomposition took place. By this procedure, it was found possible to purify 4-hydroxy-2-heptylamine and its N-monomethylated homolog. However, the presence of a side chain on the No. 3 carbon atom made the compound too unstable to withstand this treatment. Hence, 3-methyl- and 3-ethyl-4-hydroxy-2-heptylamine and their N-monomethylated homologs resisted all of the above enumerated attempts at purification. It was found that the presence of both a methyl and an hydroxyl group on the carbon atom adjacent to the oxime group prevented its hydrogenation under the conditions employed in this work. Thus neither 3-hydroxy-3-methyl-2-heptanone oxime nor 3,4-dihydroxy-3-methyl-2-heptanone oxime could be converted to the corresponding amines.

The saturated alkyl amines were prepared by the reduction of the corresponding saturated and unsaturated ketoximes and ketimines, and by the catalytic hydrogenation of mixtures of the corresponding keto alcohols and methylamine.

The unsaturated alkyl amines were prepared from the amino alcohol by treatment with concentrated hydrochloric acid. This reaction produced as its main products high-boiling neutral substances. The yield of desired compound was very low.

An interesting case of steric hindrance was noted when several attempts to react 2,2-dimethylhexanenitrile with methylmagnesium bromide were unsuccessful.

A preliminary pharmacological study³ of the pressor activity of N-methyl-4-ethyl-2-heptylamine, 4-ethyl-2-heptylamine, N-methyl-3-ethyl-2-heptylamine, N-methyl-4,4,5,5-tetramethyl-2-heptylamine, and 4,4,5,5-tetramethyl-2-heptylamine, indicated no appreciable activity. No effect on the blood pressure of cats was observed when the test samples were administered intravenously at dose levels of 0.5 and 1.0 mg. per kg. of body weight. Epinephrine in the same doses produced increases in blood pressure of 40–60 mm. which persisted for 10–20 minutes.

EXPERIMENTAL

Preparation of keto alcohols. The method used for the preparation of most of the necessary keto alcohols is a modification of previously used procedures (9, 10). It is illustrated by the preparation of 3-ethyl-4-hydroxy-2-heptanone. In the case of 3,4-dihydroxy-3-methyl-2-heptanone, a modified oxidation procedure was employed (11, 12, 13).

A. 3-Ethyl-4-hydroxy-2-heptanone. Butanal, 150 g., 2.08 moles, was slowly added to a well-stirred mixture of 300 g., 3.48 moles, of 2-pentanone, 80 ml. of ether, and 150 ml. of 15% aqueous sodium hydroxide, cooled to 15°. The mixture was stirred overnight, the organic layer separated and the aqueous layer extracted with ether. The combined ether and organic layers were neutralized with glacial acetic acid, washed with a dilute solution of sodium bicarbonate, dried over magnesium sulfate, and rectified under reduced pressure. The yield was 120 g. of 3-ethyl-4-hydroxy-2-heptanone; conversion 52%; physical constants: b.p. 99–102° (9 mm.), d_4^{20} 0.929, n_D^{20} 1.4413.

*Anal.*⁴ Calc'd for $C_9H_{18}O_2$: C, 68.32; H, 11.45.

Found: C, 67.83, 67.97; H, 11.22, 11.40.

A positive iodoform test, the point of ebullition, and the percentages by weight of carbon and hydrogen combined to eliminate the other two possible products of the reaction: 6-hydroxy-4-nonanone, b.p. estimated by analogy, ca. 120° (10 mm.); 2-ethyl-3-hydroxyhexanal, b.p. 85–87° (6 mm.) (9).

B. 3,4-Dihydroxy-3-methyl-2-heptanone. 3-Methyl-3-hepten-2-one, 52 g., 0.41 mole, and 300 ml. of water were placed in a five-liter, three-necked flask fitted with an efficient motor stirrer. Four liters of a 2% aqueous solution of potassium permanganate was added dropwise, keeping the temperature below 15°. The mixture was filtered and the manganese dioxide washed with ether. The aqueous solution was continuously extracted with ether for 12 hours. The combined extracts from 3 runs were dried over magnesium sulfate and distilled under reduced pressure. The product was a syrupy, yellow liquid of which 33 g. boiled between 116 and 120° (8–10 mm.); yield 17%; physical constants: b.p. 167–168° (758 mm.), n_D^{20} 1.4492.

Anal. Calc'd for $C_8H_{16}O_3$: C, 60.0; H, 10.0.

Found: C, 59.1, 59.5; H, 9.95, 9.70.

³ Conducted at the Abbott Laboratories.

⁴ The analyst reported that the compound volatilizes easily in the stream of oxygen but that it is hard to burn completely.

TABLE I
PROPERTIES OF AMINES AND PRECURSORS

AMINE	B.P./MM. ^g	M.P. of HCl ¹	d_4^{25}	n_D^{25}	% CON- VERSION TO AMINE FROM PARENT CPD	PARENT CPD (B.P./MM. ^g)	ANAL. OF AMINES	
							Cal'd	Found
3-Hydroxy-2-heptylamine	90-92/12 201.5/753	/	0.898 ²⁴	1.4509 ²⁵	22	2-Nitro-3-heptanol (105/7)	C 64.1 H 12.99	62.9, 63.4 12.91, 12.80
N-Methyl-3-hydroxy-2-heptylamine	67-68/4 85-87.5/8 199.5/747	/		1.4449 ²⁴	62	3-Hydroxy-2-heptyl-amine ^a	N.E. ^b 145.2	145.6, 146.8
4-Hydroxy-2-heptylamine	70/6 205/749	/	0.887 ²⁵	1.4440 ²⁵	ca. 1	4-Hydroxy-2-heptanone oxime (134/7)	N.E. ^b 131.2	132
N-Methyl-4-hydroxy-2-heptylamine	80/6 206/736	/		1.4431 ²⁵	ca. 1	4-Hydroxy-2-heptanone	N.E. ^b 145.2	144
4-Ethyl-2-heptylamine	71.5-71.9/19 174/744	83-84 ^o	0.780 ²⁵	1.4288 ²⁵	58	4-Ethyl-2-heptanone oxime (98-98.5/4)	N ^c 7.75 Cl 19.64	7.70, 7.75 19.77, 19.71
N-Methyl-4-ethyl-2-heptylamine	67-67.5/9 186/755	100-101 ^A	0.785 ²⁵	1.4321 ²⁵	14	4-Ethyl-2-heptanone	N ^c 7.22 Cl 18.30	7.15, 7.27 18.33, 18.30
4,4,5,5-Tetramethyl-2-heptylamine	89-92/11 216/755	248-249 ^A	0.831 ²⁵	1.4554 ²⁵	20	4,4,5,5-Tetramethyl-2-heptanone oxime (108-110/2-3)	N ^c 6.74 Cl 17.06	6.81, 6.75 17.10, 17.00
N,4,4,5,5-Pentamethyl-2-heptylamine	94-96/11 225/755	162-163 ^A	0.825 ²⁷	1.4509 ²⁵	10	4,4,5,5-Tetramethyl-2-heptanone	N ^c 6.31 Cl 15.98	6.33, 6.25 15.99, 15.89

2-Amino-3-ethyl-3-heptene		130-132 ^j			ca. 1	3-Ethyl-4-hydroxy-2-heptanone oxime (124-126/2)	C ^c 60.83 H 11.34	60.91, 60.79 11.19, 11.08
3-Ethyl-2-heptylamine	55-56/11 169/755		0.755 ²⁵	1.4160 ²⁵	7.2	3-Ethyl-3-hepten-2-one oxime (96-104/6)	N 9.77	10.00, 10.18
N-Methyl-3-ethyl-2-heptylamine	68-69/18 178/760	189-190 ⁱ	0.783 ²⁵	1.423 ²⁵	5	3-Ethyl-4-hydroxy-2-heptanone (99-102/9)	N ^c 7.23	7.24, 7.32
N,3-Dimethyl-2-heptylamine ^d	63/9 169.5/744	120 ^k	0.783 ²⁵	1.4255 ²⁵	9	4-Hydroxy-3-methyl-2-heptanone	N ^c 7.75 Cl 19.64	7.67, 7.69 19.63, 19.71

^a By direct methylation with methyl iodide.

^b Neutral equivalent.

^c Based on hydrochloride.

^d Hydrochloride sublimed slowly near 90° at an approximate pressure of 10⁻⁴ mm.

^e Because of possible errors due to superheating and pressure differential between flask and manometer, values given at pressures below 5 mm. are admittedly inexact. Physical characteristics of new compounds only are listed.

^f Could not prepare hydrochloride.

^g Recrystallized from petroleum ether (60-69° fraction.)

^h Recrystallized from ethyl ether methylene chloride mixture.

ⁱ Recrystallized from petroleum ether (60-69° fraction) methylene chloride mixture.

^j Recrystallized from carbon disulfide methylene chloride mixture.

^k Corrected for emergent stem. All hydrochlorides are white crystalline solids.

Preparation of α,β -unsaturated methyl alkyl ketones. The method is illustrated by the preparation of 3-ethyl-3-hepten-2-one. A single small crystal of iodine was added to 12.5 g., 0.079 mole, of 3-ethyl-4-hydroxy-2-heptanone and the liquid distilled slowly. The distillate separated into two layers. The aqueous layer was extracted with ether, the mixed oil and ether layer dried over magnesium sulfate and distilled. Nine g. of 3-ethyl-3-hepten-2-one was obtained; conversion 81%; physical constants: b.p. 59° (8 mm.), 176° (743 mm.); d_4^{25} 0.855; n_D^{25} 1.4481. M.p. of orange 2,4-dinitrophenylhydrazone 122–123°.

Anal.^a Calc'd for $C_9H_{18}O$: C, 77.1; H, 11.5.

Found: C, 73.77, 73.81; 74.74, 74.87; 74.47, 74.54; H, 11.02, 11.04; 11.20, 11.24; 10.97, 10.72.

Preparation of saturated ketones. A. 4-Ethyl-2-heptanone. 4-Ethyl-2-heptanone was prepared in 32% yield by the reaction of ethylmagnesium bromide with 3-hepten-2-one following a standard procedure (14).

B. 4,4,5,5-Tetramethyl-2-heptanone. 4,4,5,5-Tetramethyl-2-heptanone was prepared by the reaction of tertiary butylmagnesium chloride (15) with mesityl oxide following a standard procedure (16).

Preparation of oximes. The low temperature and careful adjustment of acidity were deemed necessary in the preparation of the oximes of the easily decomposed keto alcohols; they are not necessary in the other cases. The method is illustrated by the preparation of 3-ethyl-4-hydroxy-2-heptanone oxime.

Potassium carbonate, 66.4 g., 0.48 mole, dissolved in 150 ml. of water, was added to a cool (15°), well-stirred mixture of 125 g., 0.79 mole, of 3-ethyl-4-hydroxy-2-heptanone, and a solution of 68.6 g., 0.99 mole, of hydroxylamine hydrochloride in 150 ml. of water. The stirring was continued for 12 hours, during which the temperature of the reaction mixture was maintained at 20°. The very viscous organic layer was separated from the aqueous layer after dilution with 100 ml. of ether. The aqueous layer was extracted with ether and the combined ether and organic layers were dried over magnesium sulfate and distilled under reduced pressure. The product was 95 g. of 3-ethyl-4-hydroxy-2-heptanone oxime, b.p. 124–126° (2 mm.); conversion 70%.

Preparation of nitro alcohol. 2-Nitro-3-heptanol was prepared by the condensation of pentanal^b and nitroethane, with 50% conversion, by a standard method (17). The purified 2-nitro-3-heptanol had the following physical constants: b.p. 105° (7 mm.), n_D^{25} 1.4473.

Anal. Calc'd for $C_7H_{15}NO_2$: C, 52.2; H, 9.31.

Found: C, 52.1, 52.0; H, 9.31, 9.35.

Preparation of amines. A. From oximes of keto alcohols. Seventy grams of the oxime, dissolved in 100 ml. of absolute alcohol, was mixed with 7 g. of Raney nickel (18) and hydrogenated for 20 hours at room temperature under an initial pressure of 1500 lbs./sq. in. The reaction product was dried, filtered, stripped of alcohol and low-boiling amines (from decomposition of keto alcohol oxime), and rectified. Two fractions were taken, the first containing the corresponding saturated amine and the second containing the amino alcohol.

The saturated amine fraction was rehydrogenated to ensure against the presence of a small quantity of unsaturated amine (due to decomposition of amino alcohol during rectification). The amino alcohol fraction, believed to contain the corresponding diol as an impurity, was either warmed with an equivalent quantity of concentrated hydrochloric acid to yield the unsaturated amine hydrochloride, or neutralized with dilute hydrochloric acid and distilled with 1500 ml. of hexane under reduced pressure, to yield a diol-free acid solution of the amino alcohol. In either case, the free base was liberated, dried over potassium hydroxide and rectified.

^a The analysis was repeated three times on the same sample. Previous workers have reported similar difficulties with 3-hepten-2-one (9) and 3-methyl-3-hepten-2-one (10).

^b Conveniently prepared in 41% yield by dichromate oxidation of the alcohol with continuous distillation of the ternary constant boiling mixture. (ROBERTSON, "Laboratory Practice in Organic Chemistry," The McMillan Company, New York, 1937, p. 180.)

B. From methylamines of keto alcohols. A mixture of 50 g. of ketone and 30 g. of methylamine (prepared by bubbling the dry amine into the cold ketone) was mixed with 100 ml. of glacial acetic acid and hydrogenated overnight at room temperature over 7 g. of Raney nickel (18) (or 10 g. of U.O.P. nickel catalyst at 100°) at an initial pressure of 1500 lbs./sq. in. The reaction product was worked up as described under procedure A.

C. From oximes of alkyl ketones. The oximes were reduced to the amines using sodium and alcohol following a standard procedure (19).

D. From methylamines of alkyl ketones. A mixture of 0.17 mole of ketone and 20 ml. of 10 *N* aqueous methylamine solution was shaken for one-half hour. The imine was salted out with 10 g. of sodium hydroxide and dried over potassium hydroxide. It was reduced with sodium and alcohol following a standard procedure (19).

E. From nitro alcohol. A well-stirred mixture of 75 g., 0.27 mole, of ferrous sulfate heptahydrate, 45 g., 0.8 g. atom, of iron powder (100 mesh), 1.85 ml. of water, and 30 ml. of 2.3 *N* hydrochloric acid was heated with a burner until the temperature reached 100°. The burner was removed and 25 g., 0.155 mole, of 2-nitro-3-heptanol was added at such a rate as to maintain the temperature at 100°. An additional 30 g., 0.54 g. atom, of iron powder and 30 ml. of 2.3 *N* hydrochloric acid were added and the temperature returned to 100°. Another 20 g., 0.124 mole, portion of nitro alcohol was added and the solution maintained at 98° for one hour. The cooled reaction mixture was filtered to remove iron powder and 8 g. of sodium hydroxide was added to the filtrate. The precipitated iron oxides were filtered off and 40 g. of sodium hydroxide was added to the filtrate to salt out the amino alcohol. It was found more expedient to extract the amino alcohol with ether in a continuous extractor than to separate the base directly. The ether extract was dried over calcium oxide and rectified. Additional data may be found in Table I.

2,2-Dimethylhexanenitrile. 2,2-Dimethylhexanenitrile was prepared in 38% yield from 2-methylpropanenitrile⁷ and 1-bromobutane by the method of Ziegler and Ohlinger (20). The purified nitrile had the following physical constants: b.p. 57–58° (10 mm.), 171° (753 mm.), d_4^{25} 0.799, n_D^{25} 1.4091.

Anal. Calc'd for $C_8H_{16}N$: C, 76.7; H, 12.00.

Found: C, 76.0, 76.1; H, 11.65, 11.70.

ACKNOWLEDGMENT

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SUMMARY

1. A series of aliphatic compounds related to 2-heptylamine have been prepared.
2. Preliminary pharmacological studies on several of these compounds indicate no appreciable pressor activity.

LAFAYETTE, IND.

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⁷ Conveniently prepared in 51% yield from lead thiocyanate and zinc isobutyrate [VAN EBBES AND REID, *J. Am. Chem. Soc.*, **38**, 2120 (1916)].

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PREPARATION OF METHACRYLAMIDE

RICHARD H. WILEY AND WALTER E. WADDEY¹

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The present study was undertaken to develop a convenient laboratory method for the preparation of small quantities of methacrylamide. Methacrylamide has been prepared by the reaction of acetone cyanohydrin with concentrated sulfuric acid (1, 2, 3, 4, 5, 6) and by the hydrolysis of methacrylonitrile (7). Trial experiments indicated that the procedure described by Crawford and McGrath (3) was operable on a laboratory basis to give 46% yields of isolated amide. This procedure requires the following steps: (a) heat acetone cyanohydrin with concentrated sulfuric acid, (b) dilute, (c) neutralize with calcium carbonate, (d) filter off calcium sulfate, (e) evaporate to dryness, and (f) recrystallize from benzene. This isolation procedure is necessary because methacrylamide is very soluble in both water and organic solvents. It is also inconvenient and laborious and results in loss of amide through polymerization and hydrolysis. A technique has been developed for isolating the amide from the acetone cyanohydrin-sulfuric acid reaction mixture, and used to determine conditions of time and temperature which give maximum conversion of cyanohydrin to amide.

The procedure used in isolating methacrylamide from the acetone cyanohydrin-sulfuric acid mixture is based on a combined neutralization of the sulfuric acid and salting out of the amide. The feasibility of this process was demonstrated by the following experiment. Dissolving 20 g. of anhydrous sodium sulfate in a solution of 5 g. of methacrylamide in 50 ml. of water salted out 90% of the solid amide. This technique was shown to be adaptable to the isolation of methacrylamide from the sulfuric acid reaction mixture by forming the sodium sulfate through neutralization of the sulfuric acid. Thus, 17 g. of amide in 80 ml. of water and 30 g. of concentrated sulfuric acid was neutralized with 32.5 g. of sodium carbonate at below 25°. The salted out material was recrystallized from benzene to give a total of 15 g. or 88%.

With this technique of isolating the methacrylamide, one can follow the course of the conversion of acetone cyanohydrin to amide by actual isolation of the product. A series of experiments was designed to determine the effect of time and temperature on the reaction. The acetone cyanohydrin-sulfuric acid reaction mixture was heated quickly to reaction temperature, 100–150°, and sampled at 15-minute intervals. Yield of amide was determined on each sample and plotted as a function of time. The data for runs at 100, 130, and 150° are given in Figure 1. From these data it is seen that a maximum yield of 20 g. (71%) is obtained by heating at 150° for 22 minutes, 7 of which are required to reach 150°.

¹ Present address: Standard Oil Development Company, Elizabeth, New Jersey.

At each temperature there is an optimum time at which maximum yield is obtained, and after which the yield drops off. It is possible that shorter heating times at higher temperatures would give slightly higher yields than those recorded here. On the basis of an isolation which recovers 90% of the product, an isolated yield of 71% corresponds to a conversion of about 80%. The data show that the time and temperature are determining factors and reproducible operation requires careful specification of these variables. A preferred procedure based on the optimum conditions is given in the experimental part.

EXPERIMENTAL PART

Study of time and temperature variations. In a 1-liter round-bottomed flask equipped with stirrer, dropping-funnel, and thermometer were placed 300 g. of 98% sulfuric acid and 2 g. of flowers of sulfur. To this was added, over forty minutes, 170 g. (2 moles) of acetone cyanohydrin (Rohm and Haas Co.), while keeping the temperature at 70–80° by externa

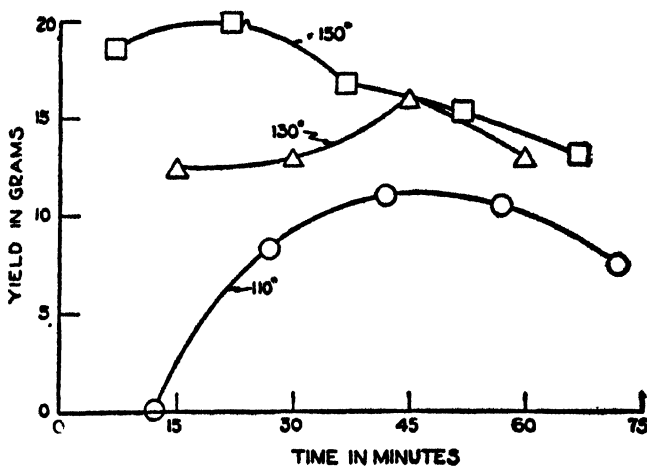


FIG. 1. Yield of methacrylamide isolated from acetone cyanohydrin-sulfuric reaction as a function of time and temperature of reaction. Theoretical yield 28.3 g.

cooling. The flask was immersed in an oil-bath preheated to 135°. Aliquot portions (78.5 g., one-sixth of total volume) were withdrawn at intervals. The methacrylamide content of each sample was determined quickly as follows. The sample was cooled to room temperature, poured into 125 ml. of cold water, filtered, and neutralized with 53 g. of sodium carbonate. The salted out solid was collected, dried, extracted with 200 ml. and two 100-ml. portions of hot benzene. The benzene extracts were treated with Norit, filtered, and cooled. The first crop of crystals was separated and the mother liquor evaporated to give a second crop. The combined weight of the two fractions was taken as the yield of amide. The theoretical yield from each portion is one-third mole, 28.3 g.

In experiments at different temperatures, the heating was varied by starting with the oil-bath preheated to 5° above the desired temperature and holding it at the desired temperature. Samples were withdrawn as the temperature rose, the first at 100–110°, when the yield was never over 7%, and then at the temperature of the run. The yield data are summarized in Figure 1. An attempt to carry out the process at 170° gave results which indicated that the highest yield was obtained at 150° before the contents of the flask reached 170°. This indicated that the procedure described is not so well suited to rapid, high temperature operations as the continuous unit used by Crawford (2).

Preferred procedure for synthesis of methacrylamide. In a 1-liter round-bottomed flask fitted with an efficient stirrer, a dropping-funnel, and a thermometer, were placed 150 g. (1.5 moles) of 98% sulfuric acid, prepared by the addition of 33.5 ml. of fuming sulfuric acid (15% SO_3) to 48 ml. of acid of sp. gr. 1.84, and 1 g. of flowers of sulfur. To this was added, with rapid stirring, 85 g. (1 mole) of acetone cyanohydrin, as prepared in Organic Syntheses (8) or as furnished by Rohm and Haas Company, over a period of 25 minutes keeping the temperature of the contents of the flask at 75–80° by cooling in a water-bath. At the end of this period, the water-bath was replaced with an oil-bath preheated to 155°. With continued stirring, the temperature of the reaction mixture was raised to 150° within 5 minutes and maintained at 150° for 15 minutes. The reaction mixture was quickly cooled to room temperature by replacing the oil-bath with an ice-bath and was then poured into 375 ml. of cold water. The diluted mixture was filtered to separate a small amount of polymer. The filtrate was neutralized and the crude product salted out of solution by adding, while holding the temperature below 30°, 160 g. of sodium carbonate. The salted out material, which rises to the top of the solution, was separated and, after drying 10–24 hours in a vacuum desiccator over calcium chloride, gave 320 g. of a light tan solid which contains some sodium sulfate.

The crude solid obtained in the preceding paragraph was placed in a 2-l. flask and heated and stirred with 500 ml. of boiling benzene. The solvent was decanted and the extraction was repeated with four 200-ml. portions of benzene. The combined benzene solutions were heated to boiling, treated with Norit, and filtered. On cooling, 50–52 g. of methacrylamide separated, m.p. 105–107°. An additional 6–8 g., m.p. 103–105°, were obtained when the mother liquor was concentrated to 150 ml. and cooled. The yield of methacrylamide was 56–60 g. (66–71% of the theoretical amount).

SUMMARY

A procedure for isolating methacrylamide from aqueous sulfuric acid solution has been developed and used in a study of the effect of time and temperature on the conversion of acetone cyanohydrin-sulfuric acid solutions to methacrylamide. In the procedure described, yields of 70% of isolated methacrylamide are obtained by heating the reaction mixture at 150° for 15 to 20 minutes.

CHAPEL HILL, N. C.

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THE STEREOCHEMISTRY OF THE *i*-STEROIDS AND THEIR TRANSFORMATION PRODUCTSR. M. DODSON¹ AND BYRON RIEGEL*Received February 2, 1948*

Although the gross structure of the steroid nucleus was elucidated in 1932 (1, 2), there has been a marked delay in the solution of many of the stereochemical aspects of the steroid structure. In particular, the stereochemistry of the replacement reactions at C-3 in steroids should be clarified. In this paper the configuration of the C-3 derivatives of cholesterol will be related to the configuration of the cholesterol by the use of stereospecific reactions, the formation and the rearrangement of the *i*-steroids. Then, after the determination of the configuration of groups at C-3 in steroids, a reasonable spacial configuration for the *i*-steroids will be postulated.

The replacement reaction at C-3 in steroids. The first extensive investigations of the replacement reaction in steroids were made by Marker (3) and by Ruzicka (4) while attempting to develop a feasible synthesis for androsterone. On the basis of a comparison of the melting points of the epimeric cholestyl chlorides with those of the epimeric cholestanols, Ruzicka suggested that a Walden inversion takes place in the formation of cholesteryl chloride from cholesterol. Bergmann (5), from a study of the replacement reaction on optically active halides with the acetate ion, took exception to this conclusion of Ruzicka. Bergmann contended that inversions take place on the treatment of the cholestyl chlorides with the acetate ion, and showed from this that the formation of cholesteryl chloride from cholesterol proceeds without inversion. Very recently Shoppee (6) has summarized the evidence on the replacement reaction in steroids and has reached the same conclusions as Bergmann on the basis of very similar evidence.

Decisive evidence that the conclusions reached originally by Bergmann are correct can be obtained from a study of the formation and rearrangement of the *i*-steroids. Some indication that the formation of *i*-cholesten-6-one (V) is stereospecific is apparent from the work of Windaus (7, 8). He found that " α "-chlorocholestan-6-one (IV) when warmed with alcoholic potassium hydroxide formed "heterocholestenone" (V), while " β "-chlorocholestan-6-one (IX) was recovered unchanged when treated under the same conditions. Since alkyl chlorides and alkyl *p*-toluenesulfonates show similar properties in replacement reactions, it was decided to study the reactions of " α " and " β "-chlorocholestan-6-one and to compare them with the reactions of the epimeric 3-*p*-toluenesulfonyloxycholestan-6-ones. In this way a correlation between the configuration of the groups at C-3 of the various 6-ketocholestanes could be obtained, and from the methods of formation of these derivatives, a correlation

¹ National Research Council Predoctoral Fellow, 1946-1947. Present address: School of Chemistry, University of Minnesota, Minneapolis, Minnesota.

between the configuration of cholesterol and cholesteryl chloride would also be established.

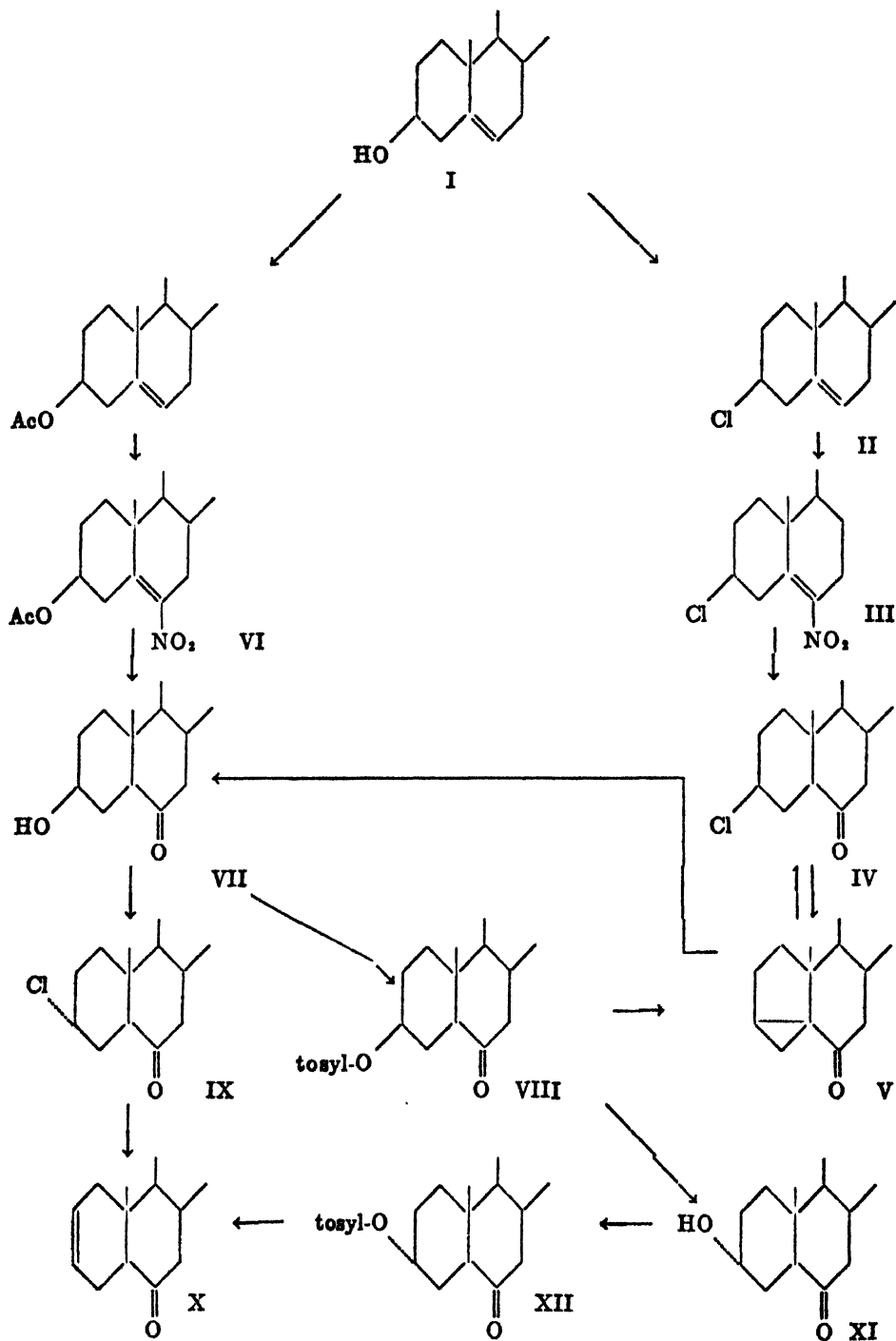
The stereochemical relationships confirmed by this work can be readily followed by reference to the chart of formulas. " α "-Chlorocholestan-6-one (IV) was easily obtained in good yield by the reduction of 6-nitrocholesteryl chloride (III) with zinc dust and acetic acid. 6-Nitrocholesteryl chloride (III), in turn, was prepared by the nitration of cholesteryl chloride (II) according to the method of Windaus and Dalmer (7). Thus in the preparation of " α "-cholestan-6-one from cholesteryl chloride, there is no possibility for inversion of the chloro group at C-3; that is, " α "-chlorocholestan-6-one has the same configuration at C-3 as cholesteryl chloride. On being heated for one hour in a 5% alcoholic potassium hydroxide solution, " α "-chlorocholestan-6-one (IV) was converted in 80–93% yield to *i*-cholesten-6-one (V) (7).

In order to prepare 3(β)-*p*-toluenesulfonylcholestan-6-one (VIII), cholesteryl acetate was first nitrated to 6-nitrocholesteryl acetate (VI) in 69–78% yields according to the method of Mauthner and Suida (9). The nitro compound was then reduced with zinc dust and acetic acid to 3-acetoxycholestan-6-one and the acetate hydrolyzed to 3-hydroxycholestan-6-one (VII) with an alcoholic solution of hydrochloric acid. The over-all yield of 3-hydroxycholestan-6-one from 6-nitrocholesteryl acetate was 91%. This preparation of 3-hydroxycholestan-6-one differs from that developed by Heilbron (10), who experienced some difficulty in preparing 3-acetoxycholestan-6-one by the directions available in the literature.

In the preparation of 3-hydroxycholestan-6-one (VII) from cholesterol (I), it is necessary to first acetylate the C-3 hydroxyl group and then to hydrolyze the acetate. However, it is well established that acid catalyzed esterification of hydroxyl groups similar to this, as well as the hydrolysis of the resulting esters, does not cleave the alkyl-oxygen bond; only the acyl-oxygen bond is broken (11). Therefore, the configuration of the group at C-3 is left unchanged by these reactions, and compound VII is correctly formulated as 3(β)-hydroxycholestan-6-one.

This compound (VII) was easily converted to its *p*-toluenesulfonate by means of *p*-toluenesulfonyl chloride in anhydrous pyridine. Since the oxygen atom attached to C-3 must be that from the alcohol, it follows that the configuration of the tosylate at C-3 must also be the same as cholesterol. When heated in a 5% alcoholic potassium hydroxide solution, 3(β)-*p*-toluenesulfonylcholestan-6-one (VIII) was converted in 85–92% yield to *i*-cholesten-6-one (V), identical with that obtained from " α "-chlorocholestan-6-one. From this, one can conclude that, if the formation of *i*-cholesten-6-one (V) is a stereospecific reaction, " α "-chlorocholestan-6-one (IV) has the same configuration as 3(β)-*p*-toluenesulfonylcholestan-6-one. It would necessarily follow from this that cholesteryl chloride has the same configuration at C-3 as cholesterol. However, the assumption that the formation of *i*-cholesten-6-one is stereospecific must be proved.

In order to establish this, 3(β)-hydroxycholestan-6-one (VII) was converted to " β "-chlorocholestan-6-one (IX) according to the directions of Windaus and



Stein (12). It had previously been reported that this compound was recovered unchanged when heated with alcoholic potassium hydroxide (8). On repetition

of this experiment, it was found that 74% of the material was recovered unchanged after heating under reflux for one hour; the remaining, more soluble material, however, had a very low melting point, 75–85°. The “ β ”-chlorocholestan-6-one (IX) was, therefore, heated under reflux for nineteen hours with a 5% alcoholic solution of potassium hydroxide. Chromatography on alumina of the resulting mixture gave a 40–49% yield of 2-cholesten-6-one (X) and no other pure compound was isolated. Ladenburg, Chakravorty, and Wallis (13) were the first to describe the preparation of the unsaturated ketone (X). However, they assigned the ethylenic bond² to the 4,5-position in conjugation with the carbonyl group.

3(α)-Hydroxycholestan-6-one (XI) was prepared by the replacement with inversion of the tosylate group in 3(β)-*p*-toluenesulfonylcholestan-6-one (VIII) by means of the acetate ion. The crude esters formed from this reaction were saponified, and the 2-cholesten-6-one, also formed in the reaction, was separated by crystallization from alcohol. The 3(α)-hydroxycholestan-6-one (XI) was then separated from the (β) isomer, which was also present, by chromatography on alumina. The structure of 3(α)-hydroxycholestan-6-one was proved by oxidation to cholestane-3,6-dione, identical with the compound obtained by the oxidation of the (β) isomer.

3(α)-*p*-Toluenesulfonylcholestan-6-one (XII), prepared from the alcohol with *p*-toluenesulfonyl chloride in pyridine, was heated under reflux with a 5% alcoholic solution of potassium hydroxide in exactly the same way as had previously been done with the (β) tosylate. Since no pure product could be isolated by repeated crystallizations, the crude material was chromatographed twice on alumina. From the 1:1 benzene-petroleum ether eluate of the second chromatogram, a 23% yield of slightly impure 2-cholesten-6-one (X) was obtained.

From these elimination reactions, one can definitely conclude that the formation of *i*-cholesten-6-one is a stereospecific reaction. Both 3(β)-*p*-toluenesulfonylcholestan-6-one (VIII) and “ α ”-chlorocholestan-6-one (IV) lose acid on treatment with alcoholic potassium hydroxide to form *i*-cholesten-6-one. The compounds epimeric with these at C-3 lost acid on similar treatment to form 2-cholesten-6-one. This naturally leads to the conclusion that 3(β)-*p*-toluenesulfonylcholestan-6-one (VIII) and “ α ”-chlorocholestan-6-one (IV) possess the same configuration at C-3. Likewise, 3(α)-*p*-toluenesulfonylcholestan-6-one (XII) and “ β ”-chlorocholestan-6-one (IX) must have the same configuration at C-3. It follows from this that no inversion has taken place in the formation of cholesteryl chloride from cholesterol. On the other hand, the action of phosphorus pentachloride on 3(β)-hydroxycholestan-6-one produces 3(α)-chlorocholestan-6-one with inversion. The trivial indices originally assigned to these chloro compounds must, therefore, be reversed. Cholesteryl chloride is actually

² The position of the carbon-carbon double bond in compound (X) was definitely established by Blunschy, Hardegger and Simon, *Helv. Chim. Acta*, **29**, 199 (1946). Although identical in all other respects, their compound did not display the ultraviolet absorption maximum at 2450 Å reported by the Princeton workers.

3(β)-cholesteryl chloride (II); " α "-chlorocholestan-6-one is 3(β)-chlorocholestan-6-one (IV); and " β "-chlorocholestan-6-one is actually 3(α)-chlorocholestan-6-one (IX).

The correlation of the optical rotatory powers of these compounds also indicates that no inversion takes place in the formation of cholesteryl chloride from cholesterol. Bernstein and co-workers (14) in a summary of their conclusions from an extensive study of the optical rotatory powers of steroids, state, "The C₃ (α)-form of any steroid will have a higher positive rotatory power (sodium light) than the corresponding (β)-form regardless of the solvent used." They indicate that the only exceptions to this rule may be in its application to Δ^5 - ϵ -stenols in solvents other than chloroform. Our data on the optical rotatory powers of C-3 substituted derivatives of cholestan-6-one are summarized in Table I. Data on the epimeric chlorocholestanes and chloroandrostanes are included for comparison. It is seen that in all of the pairs of compounds with the exception of the epimeric dinitrobenzoates, the (α)-epimer has a higher posi-

TABLE I
SPECIFIC ROTATIONS

COMPOUND	SPECIFIC ROTATION, CHCl ₃	
	(α)	(β)
3-Hydroxycholestan-6-one.....	+2.6	-5.1
3-Acetoxycholestan-6-one ...	-3.7	-15.5 ^a
3- <i>p</i> -Toluenesulfonoxcholestan-6-one	+1.1	-5.5
3-(3,5-Dinitrobenzoxy)cholestan-6-one...	-11.8	+1.7
3-Chlorocholestan-6-one	+7.7	-0.6
3-Chlorocholestan-6-one (6)	+30.5	+27
3-Chloroandrostan-17-one (6)	+94	+92

^a Plattner and Lang, *Helv. Chim. Acta*, **27**, 1872 (1944), report the specific rotation of this compound in chloroform to be -15.2° ; -13.8° .

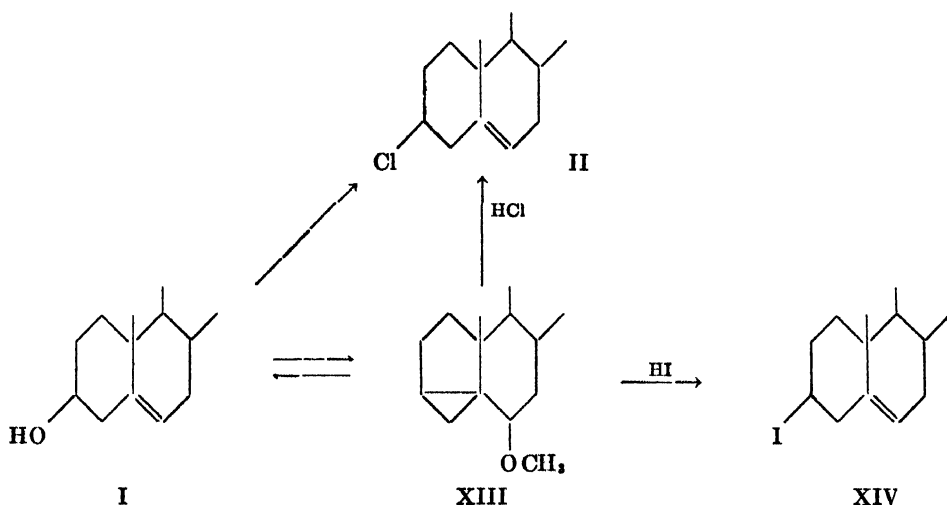
tive rotation than the (β)-epimer. It appears, however, that the epimeric 3-(3,5-dinitrobenzoxy)cholestan-6-ones are an exception to this rule postulated by Bernstein.

The opening of the cyclopropane ring. The opening of the cyclopropane ring in *i*-cholesten-6-one also leads one to the above conclusions. Wallis and co-workers (13, 15) have shown that *i*-cholesten-6-one (V) is converted to " α "-chlorocholestan-6-one (IV) with hydrogen chloride in acetic acid and to 3(β)-hydroxycholestan-6-one (VII) with sulfuric acid in acetic acid, both in very good yields. Here the same stereospecific, acid-catalyzed reaction has taken place in both cases, and one can only conclude that the configurations of the compounds formed are identical.

The rearrangement of *i*-cholesteryl methyl ether (XIII) provides further evidence that the configurations of the hydroxyl group in cholesterol (I) and of the chloro group in cholesteryl chloride (II) are the same.³ *i*-Cholesteryl methyl

³ The correlation was independently recognized by Winstein and Adams, *J. Am. Chem. Soc.*, **70**, 838 (1948).

ether (XIII), formed from cholesteryl *p*-toluenesulfonate (16), is converted to the corresponding cholesteryl halides when treated with halogen acids in acetic acid (17). The yields are excellent, showing that the reaction is stereospecific; only one isomer is obtained. The cholesteryl chloride obtained from the rearrangement with replacement is identical with that prepared from cholesterol with phosphorus pentachloride. Similarly, the cholesteryl bromide obtained



is the same as that prepared with phosphorus tribromide. The *i*-cholesteryl methyl ether (XIII) is converted back to cholesteryl acetate⁴ in good yield by refluxing it in acetic acid to which has been added a few drops of sulfuric acid. The yield for this conversion was about 80%. Since all of these reactions involve the same rearrangement with replacement, and since all of the compounds obtained are stereochemically pure, one can conclude that the configurations of all of the rearrangement products are identical. Thus the rearrangements of the *i*-steroids can be used to establish the configuration of C-3 of other sterol derivatives.

Recently, an independent determination of the configuration of the C-3 iodine in cholesteryl iodide (XIV), formed from *i*-cholesteryl ethyl ether, has been made by X-ray analysis (18). It was found that the carbon-iodine bond is *cis* to the methyl group at C-10. This, in conjunction with the preceding data, provides an independent proof of the (β) configuration of the hydroxyl group in cholesterol. This configuration was originally assigned by Ruzicka (19). It is also in agreement with Kendall's recent proof that the C-3 hydroxyl group in desoxycholic acid has an (α) configuration (20).

The spacial configuration of the *i*-steroids. The preceding information on the stereospecificity of *i*-steroid formation enables one to postulate a reasonable spacial configuration for *i*-cholesten-6-one. It has been shown by the Clemmensen reduction of cholestane-3,6-dione (21) to cholestane that the union of rings A and B in the 6-ketosteroids is *trans*; that is, the C-5 hydrogen in 3(β)-

⁴ The authors are indebted to Dr. Yin-Lin Wang for this information.

chlorocholestan-6-one has an (α) configuration. It has been shown that *i*-cholesten-6-one is formed only from the (β)-chloride or tosylate. Thus in 3(β)-chlorocholestan-6-one, the hydrogen at C-5 and the chlorine at C-3 are *trans* to each other. Michael (22) has shown that it is easier to remove halogen acid from a *trans* olefinic derivative than from the *cis* isomer; hydrogen chloride is eliminated from chlorofumaric acid about forty-eight times as rapidly as from chloromaleic acid when they are treated under similar conditions with a base. It, therefore, appears that the hydrogen at C-5 and the chlorine at C-3 in 3(β)-chlorocholestan-6-one are ideally situated for elimination.

In an elimination reaction of this type, it is highly probable that the attack of the hydroxyl ion first results in the ionization of the C-5 hydrogen atom. The pair of electrons remaining at C-5 could then attack the back side of C-3, eliminating the chlorine atom with inversion at C-3. Models show that the compound so formed has the five-membered A ring and the six-membered B ring joined in a *cis* configuration. Hückel and co-workers (23) have shown that the *cis* configuration is the most stable configuration of the hexahydroindans. Carbon-4 in the cyclopropane ring is then *cis* to the methyl group at C-10. This model can be made without any undue strain except that which is normally associated with the cyclopropane ring.

On the other hand, if an attempt is made to eliminate hydrogen chloride from the 3,5-positions of 3(α)-chlorocholestan-6-one, either a *cis* elimination would be required or inversion of the carbanion must first take place at C-5 followed by a *trans* elimination. It has already been stated that *cis* elimination takes place with much greater difficulty than *trans* elimination. If inversion of the carbanion at C-5 takes place, followed by *trans* elimination, the five-membered A ring and the six-membered B ring would be joined in a *trans* configuration. The *trans* union in hexahydroindans results in a strained ring system in which the five-membered ring is no longer completely planar.⁵ The cyclopropane ring, joined to a non-planar five-membered ring, would further increase the strain in this ring system. Considering these facts, one is not surprised that an isomeric *i*-cholesten-6-one has not been prepared by the 3,5-elimination of hydrogen chloride from 3(α)-chlorocholestan-6-one. Consideration of all of these facts also lends credence to the previous formulation of *i*-cholesten-6-one.

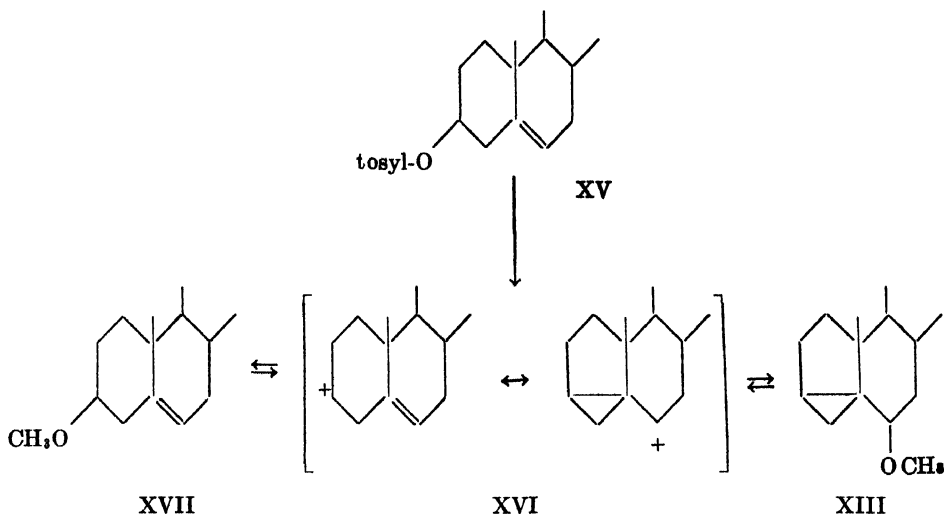
Wallis and co-workers (13, 15) and Heilbron and co-workers (24) have succeeded in converting *i*-cholesterol, formed by a rearrangement reaction, into *i*-cholesten-6-one, which is also formed by the 3,5-elimination reaction. Therefore, this same spacial configuration already assigned to *i*-cholesten-6-one should be assigned to all *i*-steroids irrespective of their method of preparation.

The mechanism of i-steroid formation and rearrangement. It should be emphasized that both the formation of *i*-cholesteryl methyl ether (XIII) from cholesteryl *p*-toluenesulfonate and the rearrangement of *i*-cholesteryl methyl ether to normal derivatives of cholesterol are stereospecific reactions. In all cases, only one of the two possible epimers has been isolated, and the yield of

⁵ Consider, for example, the five-membered D ring in cholesteryl iodide, reference (18).

product is very high. Any mechanism for *i*-steroid formation and rearrangement must account for this stereospecificity of the reaction.

Stoll (16) first demonstrated that the reaction of cholesteryl *p*-toluenesulfonate (XV) with pure methanol leads to the formation of the normal methyl ether (XVII), while reaction in methanol containing sodium acetate or pyridine leads to the formation of the isomeric methyl ether, nor formulated, as XIII



above. Winstein³ recently studied the kinetics of the reaction of cholesteryl *p*-toluenesulfonate (XV) with glacial acetic acid and found the reaction to be first order. Therefore, it is probable that in either case the first phase of the reaction of cholesteryl *p*-toluenesulfonate (XV) in methanol is the solvolysis of the tosylate to the hybrid cation (XVI), which can then react with methanol at either the C-3 or C-6 position to form the normal (XVII) or the isomeric (XIII) cholesteryl methyl ether respectively. Since in buffered solutions, where acid cleavage of either ether is eliminated, the product is primarily the *i*-methyl ether (XIII), the attack of methyl alcohol at C-6 of the hybrid cation must predominate over attack at C-3. In a buffered solution the reaction goes no further, and the predominant product is the *i*-steroid (XIII).

However, in acid solution a further reaction, the cleavage of the *i*-methyl ether, takes place. Since this ether is analogous to an allylic ether, cleavage by acids would be expected to proceed readily. Acid cleavage of the *i*-ether (XIII) would produce methanol and the hybrid cation (XVI), which would again be subject to attack by methanol at both C-3 and C-6. The normal methyl ether (XVII), on the other hand, is stable to dilute acids (17). Therefore, even though attack by methanol at C-6 predominates over attack at C-3, the normal methyl ether (XVII) would be the only product isolated from acid solution.

In order to explain the stereospecificity of these reactions, the structure of the resonance hybrid (XVI) must be examined. It is realized that the structures postulated for the resonance hybrid are not completely compatible with the

rules usually formulated for resonance hybrids (25). However, this hybrid (XVI) can be pictured as an ion with a partial but greatly distorted δ bond between C-3 and C-5 and a partial, distorted π bond between C-5 and C-6. In any case atomic orbitals from C-3 and C-6 are overlapping the orbital from C-5. If the configuration of the *i*-steroids is now considered, it follows that C-4 in the resonance hybrid (XVI) is already projecting up in a *cis* relationship to the C-10 methyl group and that the maximum electron density is on the (α) side of C-3. Attack by a nucleophilic reagent will of necessity take place at a position of minimum electron density; this must then be from the (β) side of C-3 and thus will account for the stereospecificity of *i*-steroid rearrangement.

Predication of the configuration of the methoxyl group at C-6 in *i*-cholesteryl methyl ether is difficult on the basis of this theory alone. However, from the structure of the resonance hybrid (XVI) it is clear that the π bond between C-5 and C-6 will be distorted and that this distortion will, most probably, lead to unequal electron densities on the (α) and (β) sides of C-6. The distortion of this π bond will, therefore, account for the stereospecificity of *i*-steroid formation. It is our opinion that the maximum electron density in the resonance hybrid is also on the (α) side of C-6, and that the methoxyl group at C-6 in *i*-cholesteryl methyl ether (XIII) has a (β) configuration.

This mechanism of *i*-steroid formation and rearrangement leads one to suspect that many replacement reactions at C-3 in $\Delta^5, 6$ unsaturated steroids may go through an *i*-steroid intermediate. In any case, replacement reactions at C-3 cannot be discussed without considering the possibility of *i*-steroid formation and rearrangement.

Acknowledgment. The authors wish to express their appreciation to many former associates and friends that have contributed to this problem, especially Drs. Edwin W. Meyer, Samuel Siegel, and Saul Winstein.

EXPERIMENTAL⁶

6-Nitrocholesteryl acetate (VI). This compound was prepared in 70–78% yield by the nitration of cholesteryl acetate according to the directions given by Mauthner and Suida (9). Equal weights of cholesteryl acetate and sodium nitrite were always used.

3(β)-Hydroxycholestan-6-one (VII). 6-Nitrocholesteryl acetate (20 g.) was dissolved in 400 ml. of glacial acetic acid stirred with a Hershberg stirrer. This solution was diluted with 40 ml. of water. Then 40 g. of zinc dust was added to the solution in small portions over a period of four hours. After the initial exothermic reaction had subsided (one-half hour), the suspension was heated under reflux for the remaining reaction time (three and one-half hours). The solution was then filtered and the residue washed with two 25-ml. portions of acetic acid. The filtrate was diluted with 400 ml. of water, then cooled in an ice-bath. The precipitated 3(β)-acetoxycholestan-6-one was collected by filtration. To hydrolyze the acetate, the precipitate was dissolved in 200 ml. of ethanol, 60 ml. of concentrated hydrochloric acid was added, and the resulting suspension was heated under reflux for one hour. The suspension was then cooled to 5°, filtered, and the product washed with two 50-ml. portions of cold (5°) 70% ethanol. From this reduction 15.5 g. (91%) of

⁶ We are indebted to Margaret Ledyard and Patricia Craig for the microanalyses reported in this paper. All melting points were taken on a Fisher-Johns melting point apparatus.

3(β)-hydroxycholestan-6-one, m.p. 140–141.5°, was obtained. Crystallized twice from methanol, the product melted at 142–143°, $[\alpha]_D^{25} -5.1 \pm 1^\circ$ (93.3 mg. made up to 5 ml. with chloroform, α , -0.189° ; *l*, 2 dm.). Mauthner (26) has reported the specific rotation -3.14° for this compound at 20° in ether.

3(β)-Acetoxycholestan-6-one. This acetate can be obtained directly by the crystallization from ethanol of the crude acetate isolated in the above reaction. It was also prepared by the acetylation of 3(β)-hydroxycholestan-6-one with acetic anhydride in pyridine. Crystallized twice from methanol, it melted at 127–128°, $[\alpha]_D^{25} -15.5 \pm 1^\circ$ (82.0 mg. made up to 5 ml. with chloroform, α , -0.507° ; *l*, 2 dm.).

3(β)-*p*-Toluenesulfonylcholestan-6-one (VIII). 3(β)-Hydroxycholestan-6-one (5.0 g.) was dissolved in 11 ml. of anhydrous pyridine, and 5.0 g. of pure *p*-toluenesulfonyl chloride was added to the solution. The reaction mixture was warmed slightly on a steam-bath until homogeneous, then allowed to stand overnight at room temperature. The tosylate was isolated in the usual way. After crystallization from acetone, 6.2 g. (90%) of 3(β)-*p*-toluenesulfonylcholestan-6-one was obtained. The melting point of this compound varies from 169° to 179° with the rate of heating of the melting point block; the melt becomes bright red very quickly. The pure compound, however, never melts over more than a 2° range, $[\alpha]_D^{25} -5.5 \pm 0.7^\circ$ (75.6 mg. made up to 5 ml. with chloroform, α , -0.165° ; *l*, 2 dm.).

Anal. Calc'd for $C_{34}H_{52}O_4S$: C, 73.34; H, 9.41.

Found: C, 73.55; H, 9.51.

i-Cholesten-6-one (V) from 3(β)-*p*-toluenesulfonylcholestan-6-one (VIII). A solution of 2.00 g. of 3(β)-*p*-toluenesulfonylcholestan-6-one in 100 ml. of 5% alcoholic potassium hydroxide was heated under reflux for one hour. The solution turned a light yellow. This solution was poured into 200 ml. of cold water, the resulting suspension stirred thoroughly, and the product separated by filtration. From the reaction 1.18 g. (85%) of *i*-cholesten-6-one, m.p. 96.5–97.5°, was obtained. Crystallization from alcohol raised the melting point to 97–98°, $[\alpha]_D^{25} 45.6 \pm 0.7^\circ$; $44.6 \pm 0.5^\circ$ (54.2 mg. made up to 5 ml. with chloroform, α , $+0.989^\circ$; 122.5 mg. made up to 5 ml. with chloroform, α , $+2.181^\circ$; *l*, 2 dm.). Heilbron (24) has reported the specific rotation 40.9° for *i*-cholesten-6-one at 18° in chloroform solution. A mixture of this compound with a sample of *i*-cholesten-6-one prepared from 3(β)-chlorocholestan-6-one showed no melting point depression. Yields as high as 92% of *i*-cholesten-6-one have been obtained from this *p*-toluenesulfonate.

3(β)-Chlorocholestan-6-one (IV) was prepared according to the method of Windaus and Dalmer (7). Recrystallized from ethanol, the compound melted at 129.5–130.5°, $[\alpha]_D^{25} -0.6 \pm 0.6^\circ$ (85.8 mg. made up to 5 ml. with chloroform, α , -0.021° ; *l*, 2 dm.). When heated in a 5% alcoholic solution under reflux for one hour, *i*-cholesten-6-one, m.p. 96–97°, was formed in yields ranging from 79–93%.

3(α)-Chlorocholestan-6-one (IX). 3(β)-Hydroxycholestan-6-one, when treated with phosphorus pentachloride according to the direction of Windaus and Stein (12), is converted to 3(α)-chlorocholestan-6-one, m.p. 181.5–182.5°, $[\alpha]_D^{25} 7.7 \pm 0.3^\circ$ (98.3 mg. made up to 5 ml. with chloroform, α , $+0.304^\circ$; *l*, 2 dm.).

Reaction of 3(α)-chlorocholestan-6-one (IX) with alcoholic potassium hydroxide. A solution of 0.50 g. of 3(α)-chlorocholestan-6-one in 75 ml. of 5% alcoholic potassium hydroxide was heated under reflux for one hour. The solution turned light yellow in color. The boiling solution was diluted with water until cloudy, cooled in ice, and the product separated from the solution by filtration. The product was washed thoroughly on the filter with cold methanol. From this reaction 0.37 g. (74%) of the starting material, m.p. 176.5–179.5°, was recovered. The mother liquors from the above crystallization were diluted with water, and the solid that precipitated was separated by filtration, m.p. 75–85°.

In a second experiment a solution of 0.50 g. of 3(α)-chlorocholestan-6-one in 75 ml. of 5% alcoholic potassium hydroxide was heated under reflux for nineteen hours. The resulting yellow solution was diluted with water and thoroughly extracted with ether. The ether solution was washed twice with water then evaporated to dryness. The residual yellow syrup was dried over phosphorus pentoxide under vacuum. It was then dissolved

in 30 ml. of a 1:1 mixture of benzene and petroleum ether (Skellysolve B, b.p. 60-70°) and chromatographed on a 2.5 x 12.5 cm. column of activated alumina (40 g.). The first fraction eluted with 50 ml. of a 1:1 benzene-Skellysolve B mixture contained 0.184 g. (40%) of 2-cholesten-6-one, m.p. 104.5-105.5°. No pure products were obtained from any of the other eluates. The 2-cholesten-6-one was converted to its oxime by heating with hydroxylamine hydrochloride and pyridine for one hour, m.p. 187.5-190° after crystallization from alcohol. This oxime when prepared from a sample of 2-cholesten-6-one, m.p. 103.5-104.5°, that was not chromatographically pure melted at 183.5-185.5°. Wallis (13), who first prepared 2-cholesten-6-one from 3(β)-bromocholestan-6-one, reports that the compound melts at 104-105° and its oxime melts at 184-185°. In other experiments yields of 2-cholesten-6-one as high as 49% have been obtained.

3(α)-Hydroxycholestan-6-one (XI). A solution of 2.00 g. of 3(β)-*p*-toluenesulfonyloxycholestan-6-one (VIII) and 5.0 g. of anhydrous sodium acetate in 25 ml. of glacial acetic acid was heated under reflux for seventeen hours. The resulting solution was diluted with water and thoroughly extracted with ether. The ether solution was washed first with water, then with a dilute solution of sodium bicarbonate, and finally with water. The residue obtained on evaporation of the ether was saponified by heating it under reflux for one hour with 25 ml. of 10% alcoholic potassium hydroxide. The hot, alcoholic solution was then diluted with water until cloudy and cooled in ice. The precipitate that formed was separated by filtration and washed on the filter with 8 ml. of cold methanol. In this way 0.62 g. (45%) of crude 2-cholesten-6-one, m.p. 95-100°, was isolated. One crystallization of this product from ethanol gave relatively pure 2-cholesten-6-one, m.p. and mixed m.p. 102.5-104.5°.

The mother liquors from the isolation of 2-cholesten-6-one were heated to boiling and diluted with hot water until rather cloudy. They were then cooled to 0° and the precipitate that formed was separated by filtration. From a crystallization of this precipitate from dilute methanol, 0.39 g. of the crude alcohols, m.p. 110-123°, were isolated. This material was dried thoroughly over phosphorus pentoxide under vacuum. It was dissolved in 25 ml. of benzene and chromatographed on 40 g. of alumina in a column 2.5 x 12 cm. The column was first washed free of any unsaturated material with benzene, then developed with a mixture of Skellysolve B and acetone (3:1). The Skellysolve B-acetone eluates were evaporated; the fractions melting above 155° were combined and crystallized from dilute methanol. From this reaction 0.151 g. (10.4%) of 3(α)-hydroxycholestan-6-one, m.p. 159-160.5°, was obtained; $[\alpha]_D^{25}$ 2.6 \pm 0.9° (85.3 mg. made up to 5 ml. with chloroform, α , +0.090°; *l*, 2 dm.).

Anal. Calc'd for $C_{27}H_{46}O_2$: C, 80.55; H, 11.52.

Found: C, 80.26; H, 11.82.

In order to determine whether the 2-cholesten-6-one was formed during the replacement reaction or whether it was formed in the subsequent hydrolysis, the product from a second replacement reaction was chromatographed on alumina before saponification of the esters. In this way 0.55 g. (18%) of pure 2-cholesten-6-one, m.p. 103-104.5°, was obtained showing that the 2-cholesten-6-one was definitely formed during the replacement reaction. The crude alcohols were isolated from the remaining fractions after saponification, and chromatographed as before. The Skellysolve B-acetone (4:1) eluate yielded 0.433 g. (13.5%) of 3(α)-hydroxycholestan-6-one, m.p. 160-161° after crystallization from dilute methanol. The final fraction eluted from the column with acetone after two crystallizations from methanol gave slightly impure 3(β)-hydroxycholestan-6-one, m.p. 130-135°. This compound was converted in the usual way to 3(β)-*p*-toluenesulfonyloxycholestan-6-one, m.p. and mixed m.p. 174.5-176°. It is interesting to note that the epimeric hydroxycholestanones can be separated relatively easily by chromatography on alumina; fractional crystallization of either the free alcohols or the *p*-toluenesulfonates was completely ineffective in achieving this separation.

Cholestane-3,6-dione from 3(α)-hydroxycholestan-6-one (XI). A chromic acid solution was made by the addition of 8 g. of concentrated sulfuric acid and 6 g. of crystalline sodium

dichromate to 27 g. of water (27). To a solution of 42.6 mg. of 3(α)-hydroxycholestan-6-one in 0.5 ml. of acetic acid, 0.085 ml. of the chromic acid solution was added. The resulting mixture was warmed in a water-bath at 70° for fifteen minutes. The suspension was then diluted with water, filtered, and the product washed thoroughly with water. The cholestane-3,6-dione so obtained was crystallized from dilute alcohol and washed on the filter with cold methanol. From this oxidation 32.8 mg. (77%) of cholestane-3,6-dione, m.p. 168.5–170°, was obtained. Crystallization from dilute acetic acid raised its melting point to 169.5–170.5°. A mixture with the cholestane-3,6-dione prepared from 3(β)-hydroxycholestan-6-one, according to the method of Windaus (28), showed no depression in melting point.

3(α)-*p*-Toluenesulfonylcholestan-6-one (XII). To a solution of 200 mg. of 3(α)-hydroxycholestan-6-one in 1 ml. of anhydrous pyridine was added 200 mg. of pure *p*-toluenesulfonyl chloride. The mixture was warmed on the steam-bath until homogeneous, then allowed to stand overnight at room temperature. The product was isolated in the usual way, then crystallized from methanol to give 162 mg. (59%) of 3(α)-*p*-toluenesulfonylcholestan-6-one, m.p. 145.5–147°. A second crystallization from methanol raised its melting point to 147–148°, $[\alpha]_D^{24}$ 1.1 \pm 0.5° (89.3 mg. made up to 5 ml. with chloroform, α , +0.038°; *l*, 2 dm.). In a second preparation of this tosylate a 68% yield was obtained.

Anal. Calc'd for C₂₄H₃₂O₄S: C, 73.34; H, 9.41.

Found: C, 73.47; H, 9.32.

Reaction of 3(α)-*p*-toluenesulfonylcholestan-6-one (XII) with alcoholic potassium hydroxide. A solution of 50.0 mg. of 3(α)-*p*-toluenesulfonylcholestan-6-one in 4 ml. of 5% alcoholic potassium hydroxide was heated under reflux for one hour. The clear solution immediately turned light yellow. After one hour, the solution was diluted with water and the product extracted with ether. The ether solution was washed thoroughly with water and evaporated to dryness. The residue was thoroughly dried under vacuum over phosphorus pentoxide. Since preliminary experiments had shown that no pure product could be obtained by crystallization of this residue, it was dissolved in 5 ml. of Skellysolve B and chromatographed on 10 g. of alumina in a column 1.2 x 12.5 cm. The fraction eluted with benzene weighed 16.9 mg. (49%) m.p. 83–90°. This fraction was chromatographed a second time on 5 g. of alumina. The fraction eluted with a mixture of Skellysolve B and benzene (1:1) consisted of 7.8 mg. (23%) of slightly impure 2-cholesten-6-one, m.p. 98–101°. A mixture with an authentic sample of 2-cholesten-6-one melted at 101–104°. A mixture with a portion of *i*-cholesten-6-one melted below 75°. Further eluates yielded only impure material.

3(α)-Acetoxycholestan-6-one was made by the acetylation of 3(α)-hydroxycholestan-6-one with acetic anhydride in anhydrous pyridine. After crystallization from dilute methanol, the product melted at 107–108°, $[\alpha]_D^{24}$ -3.7 \pm 1° (43.8 mg. made up to 5 ml. with chloroform, α , -0.064°; *l*, 2 dm.).

Anal. Calc'd for C₂₆H₄₂O₃: C, 78.32; H, 10.88.

Found: C, 78.56; H, 10.95.

3(α)-(3,5-Dinitrobenzoxy)cholestan-6-one was made by treating a solution of 68.1 mg. of 3(α)-hydroxycholestan-6-one in 3 ml. of pyridine with 140 mg. of 3,5-dinitrobenzoyl chloride, m.p. 66–67°. From the reaction 94.5 mg. (94%) of product, m.p. 175.5–176.5°, was obtained. Crystallization from dilute acetone failed to raise the melting point, 175.5–176.5°, $[\alpha]_D^{24}$ -11.8 \pm 0.7° (76.7 mg. made up to 5 ml. with chloroform, α -0.362°; *l*, 2 dm.).

Anal. Calc'd for C₂₄H₃₄N₂O₇: C, 68.43; H, 8.11; N, 4.70.

Found: C, 68.25; H, 8.20; N, 4.58.

3(β)-(3,5-Dinitrobenzoxy)cholestan-6-one was prepared from 3(β)-hydroxycholestan-6-one according to the directions given by Shriner and Fuson (29) for the preparation of dinitrobenzoates. After crystallization from acetone, the compound melted at 234–235°, $[\alpha]_D^{24}$ +1.7 \pm 0.4° (72.9 mg. made up to 5 ml. with chloroform, α , +0.050°; *l*, 2 dm.).

Anal. Calc'd for C₂₄H₃₄N₂O₇: C, 68.43; H, 8.11; N, 4.70.

Found: C, 68.74; H, 8.30; N, 4.84.

SUMMARY

It has been shown that the formation of *i*-cholesten-6-one is a stereospecific reaction. Both 3(β)-*p*-toluenesulfonylcholestan-6-one and 3(β)-chlorocholestan-6-one form *i*-cholesten-6-one on treatment with alcoholic potassium hydroxide. The (α)-isomers form 2-cholesten-6-one on similar treatment.

From the methods of preparation of 3(β)-*p*-toluenesulfonylcholestan-6-one and 3(β)-chlorocholestan-6-one, and the stereospecificity of the formation of *i*-cholesten-6-one, it was concluded that no inversion of configuration is involved in the formation of cholesteryl chloride from cholesterol.

Further data justifying this assignment of configuration were obtained from the specific rotations of the compounds.

It was indicated that the transformation of either *i*-cholesteryl methyl ether or *i*-cholesten-6-one to normal steroids results in a (β) configuration of the groups at C-3.

The above conclusions in conjunction with the complete X-ray analysis of cholesteryl iodide provide independent proof that the C-3 hydroxyl group in cholesterol has a (β) configuration.

On the basis of the known configuration of 3(β)-chlorocholestan-6-one and 3(β)-*p*-toluenesulfonylcholestan-6-one, a spacial configuration has been assigned to *i*-cholesten-6-one.

A mechanism has been postulated for the formation and rearrangement of the *i*-steroids that accounts for the stereospecificity of the reaction. It has been suggested that many of the replacement reactions at C-3 in cholesterol go through an *i*-steroid intermediate.

EVANSTON, ILLINOIS

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ARSENICALS. PART II. DERIVATIVES OF N¹-(*p*-ARSONOBENZYL)-SULFANILAMIDE

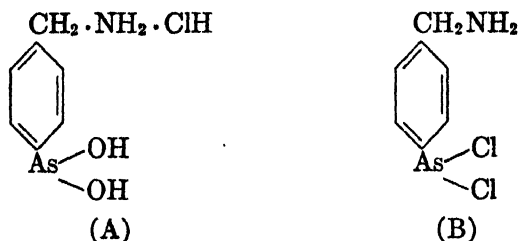
H. HERBERT FOX

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In a previous paper (1), the author described the preparation of compounds containing substituted benzenesulfonyl groups linked to aromatic arsenicals *via* an oxygen or nitrogen bridge. The present study is an extension of that work and concerns the preparation of sulfanilamido derivatives of *p*-arsonobenzylamine (homoarsanilic acid) and their reduction products.

Since the interposition of a methylene group between the para-amino group and the benzene nucleus of sulfanilamide resulted in a compound of marked therapeutic value (Marfanil), it was hoped that a similar interposition in the arsanilic acid molecule might also result in therapeutically interesting compounds. Some indication of the validity of this thesis was found in the results obtained by Eagle and his co-workers (2), who first tested *p*-arsenosobenzylamine and its acetyl derivative, and found them to be strongly trypanocidal but inferior to Mapharsen in trepanemicidal:toxic ratios.

In the present study, benzylamine was acetylated with acetic anhydride and the acetylation mixture was added to fuming nitric acid in the cold to give, predominantly, *p*-nitrobenzylacetamide (I). The *p*-nitro compound was then catalytically reduced to *p*-aminobenzylacetamide (II). The amine, upon subjection to the Bart reaction (4), gave N-(*p*-arsonobenzyl)acetamide (III), in the form of white needles. Reduction of the arsonic acid yielded N-(*p*-arsenosobenzyl)-acetamide (V) and its deacetylation gave *p*-arsonobenzylamine (IV). The latter compound was then reduced with sulfur dioxide and potassium iodide in dilute hydrochloric acid solution to give directly *p*-arsonosobenzylamine hydrochloride (formula A)



Formula A—Calc'd, As = 29.8; Cl = 14.9. Found, As = 29.8; Cl = 14.1.

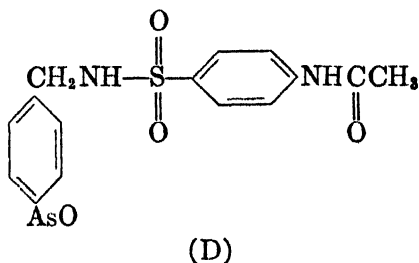
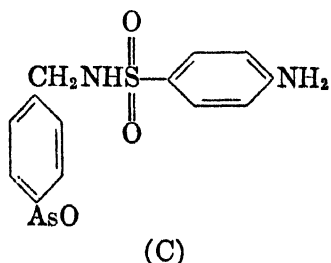
Formula B—[Doak (3)], Calc'd, As = 29.7. Found, As = 29.6.

Doak and his co-workers (3) reduced *p*-arsonobenzylamine with the same reagents and isolated a compound which they regarded as the arsen dichloride, and which they characterized as being completely resistant to hydrolysis with sodium bicarbonate. They further stated that, "the arsenoxide could be obtained only by

hydrolyzing with sodium hydroxide solution." Formula (B), deduced from the empiric formula assigned to the arsenidichloride, cannot be regarded as a likely structure since the coexistence of the highly basic free amino group and the alkali-sensitive arsenidichloride moiety is improbable. Furthermore, it was found that the reduction product obtained in these laboratories contained one atom of chlorine, even when the reduction was carried out in the presence of 3 *N* hydrochloric acid. It is most probable, therefore, that Doak and his co-workers had actually obtained *p*-arsonosobenzylamine hydrochloride (formula A) rather than the arsenidichloride. On the basis of the structure presented by formula A, the resistance to hydrolysis with sodium bicarbonate noted by those investigators, was due to the inability of the bicarbonate ion to decompose the benzylammonium chloride. When sodium hydroxide was used, they obtained *p*-arsonosobenzylamine. In these laboratories, concentrated ammonium hydroxide was used instead of sodium hydroxide and a hydrated modification of *p*-arsonosobenzylamine was obtained which melted at 142.5°.

Upon treatment of *p*-arsonobenzylamine with *p*-acetamidobenzenesulfonyl chloride in the presence of alkali, *N'*-(*p'*-arsonobenzyl)-*p*-acetamidobenzene-sulfonamide (VIII) was obtained. This compound was reduced with phenyl hydrazine to give the corresponding arsenoxide (IX). Compound VIII was deacetylated according to the method of Kwartler (5) to give *N*¹-(*p*-arsonobenzyl)-sulfanilamide (X) which on reduction with phenylhydrazine yielded the arsenoxide (XI). The reduction of the arsonic acids VIII and X with sodium hydrosulfite gave respectively *N,N'*-(*p'*-arsonobenzyl)-bis-(*p*-acetamidobenzene-sulfonamide) (XII) and *N,N'*-(*p'*-arsonobenzyl)-bis-(*p*-aminobenzenesulfonamide) (XIII).

Chemotherapeutic studies by R. J. Schnitzer of these laboratories confirmed the results obtained by Eagle (2) anent the activities of *p*-arsonosobenzylamine and its acetyl derivative. All of the sulfanilamido derivatives possessed varying degrees of spirochetocidal and/or trypanocidal activity but none of them were outstandingly effective. The arsenoxides *N*¹-(*p*-arsonobenzyl)sulfanilamide (formula C) and its acetylated derivative (formula D)



both showed good spirochetocidal activity combined with low toxicity and had chemotherapeutic indices comparable to that of Mapharsen in mouse relapsing fever.

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The author is also indebted to Dr. A. Steyermark for the microanalyses.

EXPERIMENTAL

All melting points are corrected.

I. p-Nitrobenzylacetamide. The procedure of Amsel and Hofmann (6) was modified as follows: To 216 g. of benzylamine was added dropwise 207 g. of acetic anhydride. The mixture was then refluxed for $\frac{1}{2}$ hour to ensure complete acetylation. The cooled mixture, consisting of benzylacetamide in acetic acid solution was then added dropwise with stirring to 800 cc. of fuming nitric acid (sp. gr. 1.49-1.50) at 0°. Stirring was continued at 0° for 2 $\frac{1}{2}$ hours after addition was complete. The mixture was poured onto 1000 g. of ice and was neutralized with concentrated ammonium hydroxide. On cooling the hot solution, the product precipitated out. Recrystallization from dilute alcohol resulted in pale yellow plates melting at 130-131°; yield 199 g. [Literature m.p. 125° (6) 133° (7)].

Iia. p-Aminobenzylacetamide. A solution of 188 g. of the nitro compound in ethyl alcohol was reduced with hydrogen in the presence of Raney nickel at 200 lb. pressure and room temperature. The product was obtained in quantitative yield. Upon recrystallization from benzene it precipitated in the form of near-white needles and plates melting at 93-95° [Doak (3) 85-86°].

Anal. Calc'd for $C_9H_{12}N_2O$: C, 65.7; H, 7.3; N, 17.1.

Found: C, 66.0; H, 7.6; N, 17.2.

Iib. p-Aminobenzylacetamide dihydrochloride. The reduction of the nitro compound may also be effected as follows: Forty grams of the nitro compound dissolved in 50 cc. of concentrated hydrochloric acid and 300 cc. of water was reduced at room temperature and 500 lbs. hydrogen pressure with 4 g. of palladium charcoal (wet) (10% Pd). The reaction mixture was filtered and most of the solvent was distilled off under vacuum. The residue, upon stirring with acetone yielded 20 g. of the dihydrochloride m.p. 186-189°.

Anal. Calc'd for $C_9H_{12}N_2O \cdot 2HCl$: C, 45.6; H, 6.0; N, 11.8.

Found: C, 45.5; H, 6.4; N, 12.3.

III. N-(p-arsonobenzyl)acetamide. Because of some discrepancies with the results obtained by Doak (3) the synthesis of this and the succeeding compound (IV) are given in specific detail.

Seventy-eight and one-half grams of *p*-aminobenzylacetamide dissolved in 600 cc. of 6 *N* hydrochloric acid was diazotized with 33 g. of sodium nitrite in 200 cc. of water. The diazotized solution was added to a mixture consisting of 189 g. of sodium meta arsenite, 50 cc. of 2 *N* copper sulfate, 3 l. of water and 6 l. of ice. The reaction mixture was stirred and 6 *N* sodium hydroxide was added to slight alkalinity. When the evolution of nitrogen ceased, the reaction mixture was warmed to 45° for one hour, treated with Norit, and filtered. The filtrate was acidified with concentrated hydrochloric acid to pH 3 (Congo Red) and was evaporated to dryness under a vacuum. The residue was extracted several times with hot methyl alcohol, and the combined extracts were evaporated to dryness. The crystalline residue was dissolved in 6 *N* sodium hydroxide, treated with Norit, filtered, and the filtrate adjusted to pH 3 with dilute hydrochloric acid. The resulting precipitate of crude *N*-(*p*-arsonobenzyl)acetamide weighed 58 g. On recrystallization from hot water, white needles were obtained which did not melt below 300°. Doak (3) described the compound as an amorphous powder.

Anal. Calc'd for $C_9H_{12}AsNO_4$: As, 27.4. Found: As, 27.5.

IV. p-Arsonobenzylamine. A solution of 50 g. of the acetyl compound in 132 cc. of 6 *N* sodium hydroxide was refluxed for 2 hours. The reaction mixture was diluted with an equal volume of water, filtered, and adjusted to pH 6 with acetic acid. A crystalline precipitate [Doak (3) obtained an amorphous powder] appeared, which was insoluble in water and all organic solvents and was soluble only in acids or bases. On reprecipitation from alkali with acetic acid the product was obtained as white needles which did not melt below 300°.

Anal. Calc'd for $C_7H_{10}AsNO_2$: As, 32.4. Found: As, 32.2.

V. N-(p-arsenosobenzyl)acetamide. A solution of 5 g. of the arsonic acid and 0.1 g. of potassium iodide in 100 cc. of 2 *N* hydrochloric acid was treated with sulfur dioxide for sev-

eral hours. The gummy yellow precipitate was filtered off and purified by reprecipitation from dilute sodium hydroxide with dilute acetic acid; white microcrystalline material, m.p. 223–226° [Doak (3) m.p. 224–226°].

Anal. Calc'd for $C_7H_{10}AsNO_2$: Mol. wt., 239. Found: Mol. wt., (iodine titration), 242.

VI. *p*-Arsonosobenzylamine hydrochloride. A stirred solution of 60 g. of *p*-arsonobenzylamine and 1 g. of potassium iodide in 500 cc. of 2 *N* hydrochloric acid was treated with sulfur dioxide at room temperature for 45 minutes. The mixture was then cooled to 0° with stirring and continued sulfur dioxide addition for three more hours. The white precipitate was filtered off, washed with a little cold water and then with acetone, and dried. A further quantity of the product was obtained by saturating the filtrate in the cold with sulfur dioxide and permitting it to stand in the refrigerator overnight; total yield of white microcrystalline powder, 46 g. The product did not melt below 300°.

Anal. Calc'd for $C_7H_{10}AsNO_2 \cdot HCl$: As, 29.8; Cl, 14.9; Mol. wt., 251.5.

Found: As, 29.8; Cl, 14.1; Mol. wt., (iodine titration), 244.

VII. *p*-Arsonosobenzylamine. The hydrochloride prepared above was suspended in cold concentrated ammonium hydroxide, filtered, and washed with a little cold water and then with acetone. The white powder melted at 142.5° [Doak (3) reported the anhydrous (arsenoso) modification: As = 38.0%].

Anal. Calc'd for $C_7H_{10}AsNO_2$: As, 34.9; mol. wt., 215.

Found: As, 34.5; Mol. wt., (iodine titration), 212.

VIII. *N*¹-(*p*-arsonobenzyl)-*p*-acetamidobenzenesulfonamide. To 7 g. of *p*-arsonobenzylamine in 50 cc. of 2 *N* sodium hydroxide was added 9 g. of *p*-acetamidobenzenesulfonyl chloride in acetone solution. The mixture was warmed on the steam-bath for a few minutes, filtered, diluted with water, and finally adjusted to pH 3. The product precipitated out and on recrystallization from dilute methyl alcohol was obtained in the form of glistening white plates which melted with decomposition at 300°.

Anal. Calc'd for $C_{13}H_{17}AsN_2O_6S$: As, 17.5. Found: As, 17.8.

IX. *N*¹-(*p*-arsenosobenzyl)-*p*-acetamidobenzenesulfonamide. A mixture of 5 g. of the arsonic acid and 4.2 g. of phenylhydrazine in methyl alcohol was refluxed until the evolution of nitrogen ceased. The methyl alcohol was removed and the oily residue was treated with a slight excess of 1 *N* sodium hydroxide and extracted with ether. The aqueous layer was filtered and treated with a concentrated ammonium chloride solution to yield the desired product; white powder, m.p. 215–219°; soluble in methyl alcohol, acetone, and dilute hydrochloric acid.

Anal. Calc'd for $C_{13}H_{15}AsN_2O_6S \cdot 2.5 H_2O$: As, 17.1; Mol. wt., 439.

Found: As, 16.9; Mol. wt., (iodine titration), 435.

X. *N*¹-(*p*-arsonobenzyl)sulfanilamide. Four grams of the corresponding acetyl compound was hydrolyzed according to the method of Kwartler (5). Upon recrystallization from water glistening feathery white needles were obtained, decomp. 307–308°; soluble in hot water and hot methyl alcohol and insoluble in acetone and ether. The compound gave a coupling reaction indicating the presence of the free amino group.

Anal. Calc'd for $C_{13}H_{15}AsN_2O_6S \cdot H_2O$: As, 18.6. Found: As, 18.7.

XI. *N*¹-(*p*-arsenosobenzyl)sulfanilamide. A methyl alcohol solution of 7.5 g. of the arsonic acid was reduced with phenylhydrazine as described above to yield a white powder, m.p. 122–124°.

Anal. Calc'd for $C_{13}H_{13}AsN_2O_4S \cdot 2H_2O$: As, 19.3; Mol. wt., 388.

Found: As, 18.8; Mol. wt., (iodine titration), 372.

XII. *N,N'*-(*p*-arsonobenzyl)-bis-(*p*-acetamidobenzenesulfonamide). Five grams of the arsonic acid was reduced with sodium hydrosulfite in the customary manner to yield the yellow powder characteristic of the arsonobenzenes. Since the product was insoluble in all the common solvents, it could not be purified; m.p. indefinite.

Anal. Calc'd for $C_{20}H_{20}As_2N_4O_6S_2$: As, 19.8. Found: As, 18.0.

XIII. *N,N'*-(*p*-arsenosobenzyl)-bis-(*p*-aminobenzenesulfonamide). Reduction of the cor-

responding arsonic acid with sodium hydrosulfite resulted, as above, in a yellow amorphous precipitate which could not be purified; m.p. indefinite.

Anal. Calc'd for $C_{10}H_{10}As_2N_2O_4S_2$: As, 22.3. Found: As, 23.2.

SUMMARY

Some sulfanilamido derivatives of *p*-arsonobenzylamine, and their reduction products are described in this report.

The preparation of *p*-arsonosobenzylamine and its hydrochloride are also described.

None of the compounds were outstandingly active against trypanosome and spirochetal infections though the sulfanilamido derivatives of *p*-arsonosobenzylamine possessed chemotherapeutic indices comparable to that of Mapharsen in relapsing fever experiments.

NUTLEY, N. J.

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INVESTIGATION OF THE CHEMICAL CONSTITUENTS OF BRAZILIAN SASSAFRAS OIL

MICHAEL J. HICKEY

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This oil is commonly called *Ocotea Cymbarum* [H. B. K.] and *Ocotea pretiosa* Benth. and Hook f (Fam. Lauraceae). The earlier literature (1) also describes an oil from the wood of *Cryptocaria pretiosa* Mart., but this designation is falling into disuse as a generic name in favor of *Ocotea pretiosa* (the essential oil described, however, was rich in alcohol calculated as linalool and hence it is not similar to the present-day oil of commerce).

E. Guenther (2), in an effort to clarify the botany of this oil observed the steam distillation of the wood in Brazil, and claims that according to reliable private information the product is derived from *Ocotea pretiosa* Benth. and Hook f (Fam. Lauraceae).

A. A. Dodge (3) agrees with this taxonomy in a recent paper discussing the odor and flavor similarity between this variety and the sassafras officially recognized in the U.S.P. XIII.

The purpose of the present investigation is to show the qualitative and to some extent the quantitative relationship between the U.S.P. XIII product [*sassafras albidum* (Nuttall) Nees (Fam. Lauraceae)] and the imported oil which has not been chemically investigated. A tabulation follows showing the composition relationship between the two products. The official product was also investigated in the laboratories of Fritzsche Brothers, Inc. (4). It is worth while to note the fact that the identified optically active compounds in the Brazilian oil are levorotatory, while those in the *Sassafras albidum* (Nuttall) Nees (Fam. Lauraceae) are dextrorotatory.

The product used in the investigation was imported from Brazil in December 1944. It represented oil derived from the trunk and large branches of the tree, and had been recently distilled. The preliminary chemical and physical properties follow: d_{15}^{20} 1.076; n_D^{20} 1.5350; α_D^{20} -1.42° ; solubility 20° , 2.0 volumes of 90% alcohol, opalescent in 10.0 volumes; congealing point $+9.0^\circ$; acid number 0.3; ester number 5.0; ester number after acetylation 9.0; aldehyde calculated as furfural, less than 0.1%. All of these properties are normal for commercial oil.

In order that handling would be facilitated, a primary fractionation of 45.4 kg. in a commercial still with a six-foot column was resorted to; all vapors were condensed at a temperature below $+10.0^\circ$. The oil was fractionated and analyzed as shown in Table II.

EXPERIMENTAL

Fraction I

The forerun (Fraction I) was then subdivided by fractionation at 759 mm. through an electrically heated 36-inch column of the Young type. This column had 22 discs and bulbs. The main subfractions are described below.

Identification of valeraldehyde (Ia). This consisted of 0.05% of Fraction I and distilled at 101–103°. A portion of an aqueous suspension was subjected to an alkaline 0.5% solution of sodium nitroprusside and gave a violet-red color which disappeared.

The fraction had a harsh odor. A 2,4-dinitrophenylhydrazone was prepared; it melted at 97–98° and showed no depression when mixed with a similar derivative prepared from a known sample of *n*-valeraldehyde.

TABLE I
COMPARISON OF CONSTITUENTS OF THE OILS OF BRAZILIAN AND AMERICAN SASSAFRAS

	OCOTEA PRETIOSA, %	SASSAFRAS ALBIDUM, %
Safrol	92.9	80
α -Pinene	(1) 0.7	less than 10
Phellandrene		less than 10
<i>d</i> -Camphor		6.8
Eugenol	0.6	0.5
<i>n</i> -Valeraldehyde	0.001	
Furfural	0.17	
Cineol	0.21	
Benzaldehyde	0.03	
Sesquiterpenes, high-boiling constituents and residue	circa 5.1	3

TABLE II
PHYSICAL AND CHEMICAL PROPERTIES OF THE MAIN FRACTIONS

	FRACTION I	FRACTION II	FRACTION III
Percent (by weight) of original oil	2.1	92.2	4.4
Boiling range, °C.	up to 91° 4 mm.	91.0–91.5 4 mm.	above 91.5 4 mm.
d_{15}^4	0.941	1.103	1.051
α_D^{20}	–17°13'	–0°27'	–4°2'
n_D^{20}	1.4860	1.5379	1.5283
Aldehyde as furfural ^b	10.0%	0.0%	0.0%
Acid number	0.7	0.0	30.1
Ester number	3.0	0.0	0.1
Ester number after acetylation ^c	3.1	0.0	30.6
Congealing point		+10.8°	

^a Distillation began at atmospheric pressure and was gradually reduced to 4 mm.

^b National Formulary, Second Supplement, p. 97.

^c E. Gildemeister & F. Hoffmann, "Die Ätherische Öle," 3rd ed. 1928, p. 724.

An unidentified compound (Ib). On continued distillation at 759 mm., a liquid that distilled at 129–132° was collected (0.8% of Fraction I). The fraction did not yield a derivative. This liquid darkened on standing.

Identification of l- α -pinene (Ic). This fraction, representing 33.0% of Fraction I, was distilled over metallic sodium at 155–160.0° at 760 mm. The following physical properties were determined: d_{15}^4 , 0.860; n_D^{20} , 1.4673; α_D^{20} , –40° 53'.

When *l*-pinonic acid was prepared (5) the semicarbazone melted at 203.5–204.5° and showed no depression in melting point when mixed in equal quantity by weight with pinonic acid prepared from the pinene fraction of commercial turpentine.

Identification of furfural (Id). The fraction that distilled from 160–165° at 759 mm. (8.1% of Fraction I) had a strong wood-like odor and darkened to a light brown on standing. The color was removed by washing with water; the aqueous solution was then extracted with ether. It gave an intense red color with an aniline acetate-acetic acid solution. A *p*-nitrophenylhydrazone derivative was prepared; it melted at 153–154°. No depression was noted on a mixed melting point with the *p*-nitrophenylhydrazone prepared from commercial furfural.

Identification of cineol (Ie). Progressive distillation led to a fraction that distilled at 170–180° at 760 mm. This fraction showed partial reaction with alcoholic hydroxylamine hydrochloride.

The fraction amounting to about 11.5% of Fraction I was treated with a 20% sodium bisulfite. The oil layer was separated from the aqueous solution, dried with sodium sulfate and redistilled over sodium. It yielded an *o*-cresol addition compound that melted at 55.5–56.5°, after being washed with five 200-ml. portions of water at 5°. A mixed melting point with cineol *o*-cresol addition compound showed no depression. This cineol addition compound was prepared from an Oil Eucalyptus USP XIII grade and mixed with an equal (by weight) portion of the compound prepared from the unknown.

Identification of benzaldehyde (If). The sodium bisulfite solution from above was washed with ether and the reacting compound regenerated with 3% aqueous KOH solution; the oil layer was taken up in ether. After evaporation of the ether, 1.5% of Fraction I remained. The 2,4-dinitrophenylhydrazone of this residue melted at 237° and was not depressed on mixing with the 2,4-dinitrophenylhydrazone of a synthetic commercial benzaldehyde.

An unidentified compound (Ig). This fraction (12.2% of Fraction I) had a camphoraceous odor. It distilled at 215–225° at 758 mm. On alkaline permanganate oxidation, it gave a minute amount of acid which melted at 163.5–164.5° on recrystallization from chloroform. Unsuccessful efforts to produce a camphor derivative were made (6, 7). The neutralization equivalent of the acid was 146.¹

The next part of this fraction distilled at 231.0° at 756 mm. and amounted to 35.0% of Fraction I. It was added to Fraction II because of its similarity in physical and chemical properties.

Fraction II

With this addition, Fraction II amounted to 92.9% of the total oil. The physical and chemical properties correspond to those of safrol (see Table II). A picrate was prepared which melted at 104–105.2° and when this derivative was mixed with one prepared from the safrol of *Sassafras albidum*, no depression of melting point was noted.

Fraction III

(IIIa). The forerun of this fraction (20.1% of the fraction) was identified as safrol.

Identification of eugenol (IIIb). The fraction distilling at 118–120° at 6 mm. (13.6% of Fraction III) had a spicy clove-like odor. This oil was washed with 6.5% NaOH aqueous solution; the non-reacting globules of oil were extracted with benzene. A 5% solution of sulfuric acid was used to regenerate the reacting chemical from the washed aqueous solution. Recovery was made with ether and after the evaporation of this extractant, an oil that distilled from 251–253.0° at 759 mm. was recovered. Two derivatives were made. The eugenolglycolic acid (4-allyl-2-methoxyphenoxyacetic acid) was recrystallized from dilute alcohol and melted at 96.5–97.5°. A benzoate was prepared which melted at 68.5–69.5°. Neither showed depression on a mixed melting point with the corresponding derivative prepared from the eugenol fraction of Madagascar clove oil.

An unidentified hydrocarbon (IIIc). The remaining fraction was further subdivided, 60.2% of the total distilled from 110–114° at 1 mm. Two carbon-hydrogen determinations²

¹ A greater quantity of these compounds will be isolated and further work on identification and structure will be undertaken.

² Carbon-hydrogen analyses by Miss L. Baker, Columbia Univ. N. Y. C., N. Y.

indicated that the ratio of carbon to hydrogen was 15:24 which is the ratio of these elements in the sesquiterpene series. A derivative was not obtained.¹

(IIIId). A dark blue residue with a "tarry" odor remained in the flask, representing 14.1% of Fraction III. It was tested for azulene (8) but none was detected; however, the compound gave a light green color in phosphoric acid-glacial acetic acid solution (equal parts by weight).¹

SUMMARY

This investigation led to the conclusion that *Ocotea pretiosa* Benth & Hook f (Fam. Lauraceae) contains the following constituents: *n*-valeraldehyde, *l*- α -pinene, furfural, cineol, benzaldehyde, safrol, and eugenol.

An unknown compound with a camphoraceous odor was found as was a hydrocarbon (probably a sesquiterpene).¹

NEW YORK 11, N. Y.

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STUDIES IN THE ACRIDINE SERIES. V. α -AMINO CARBINOLS
DERIVED FROM N,X-DIACETYL-9,10-DIHYDROACRIDINE¹

LEWIS J. SARGENT AND LYNDON SMALL

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That certain α -(dialkylaminomethyl)-4-quinolinemethanols, as well as naphthalene, phenanthrene, and piperidyl amino carbinols are variously effective in controlling some types of avian malarial infections has been amply demonstrated (1).

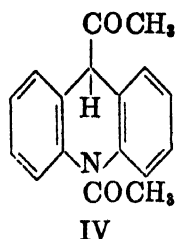
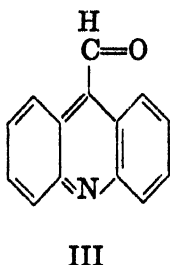
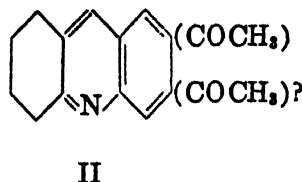
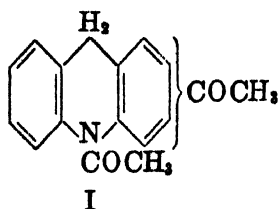
In view of the known, important, pharmacological properties of certain acridine derivatives (*e.g.*, atabrine, acriflavine), it seemed desirable to synthesize and investigate the plasmodicidal properties of diverse acridyl amino carbinols. It occurred to us that the latter could be obtained by condensing the requisite acridyl- ω -halomethyl ketones with secondary amines, followed by reduction of the resulting amino ketones to the amino carbinols. Thus far we have prepared four distinct types of these substances in which the amino carbinols may be regarded as being derived from: (I) N,x-diacetyl-9,10-dihydroacridine, (II) 6(?) and 7-acetyl-1,2,3,4-tetrahydroacridine, (III) 9-formylacridine through condensation with 3-dialkylamino-1-propylmagnesium chloride, and (IV) N,9-diacetyl-9,10-dihydroacridine. This contribution concerns itself with the first (I) of the four types mentioned; reports on the others will follow.

The idea of preparing acridyl amino carbinols is not new. As early as 1935, Eisleb (2), seeking to synthesize quinine analogs in the acridine series, prepared 9-acridyl methyl ketone by treating acridine-9-aldehyde with methylmagnesium iodide, followed by chromic acid oxidation of the resulting secondary carbinol. Interaction of the ketone in 40% HBr with bromine gave the ω -bromo ketone hydrobromide, but the latter failed to react with piperidine as expected. The failure of this condensation was unfortunate. Had it succeeded, a path would have been opened for the preparation of acridine derivatives in which the secondary carbinol group is attached to the carbon function *para* to the hetero nitrogen atom, a configuration present in, and forming an integral part of, the quinine structure. As far as can be ascertained, no further work along these lines was attempted by Eisleb.

More recently, Braz (3) reported the synthesis of several 9-acridyl- ω -halomethyl ketones. Starting with the requisite acridine-9-carboxylic acid he prepared, in turn, the acid chloride, diazo ketone and halomethyl ketone by standard procedures. Whether these halomethyl ketones were brought into reaction with amines was not disclosed, though it seems logical to infer that they were prepared for this purpose in view of the earlier experiments of Eisleb. The failure of

¹ This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the National Institute of Health. Communication XXVI in the series "Attempts to Find New Antimalarials." The Survey Numbers (SN) correspond to those given by Wiselogle (1).

Eisleb's bromo ketone to react with piperidine, in addition to certain other anomalous observations described in his paper, points up the, as yet, unexplained, unique behavior of both elementary and group substituents attached to the meso position in acridine. A parallel observation in the anthracene series was made recently in this Laboratory by May and Mosettig (4), who found that 9-*ω*-bromoacetylanthracene failed to react with secondary amines under standard conditions.



In view of Eisleb's results, it was decided to explore a different approach in the preparation of acridyl halomethyl ketones. Very little appears to be recorded in regard to the Friedel-Crafts acylation of acridine or its derivatives. It is known that heterocyclic nitrogen compounds, with some exceptions, are not readily acylated by the Friedel-Crafts reaction. Thus pyridine and quinoline either do not react at all or, when forced, yield intractable products. The presence of certain substituents in the molecule, however, (notably hydroxyl or methoxyl) appears to facilitate acylation (5, 6, 7). Carbazole, an exception to the rule regarding heterocyclic nitrogen compounds, is readily acylated by acetyl chloride (AlCl_3) to give the 3,6-diacetylcarbazole (8). The acylation of N-acetylcarbazole takes a different course, however, and N,2-diacetylcarbazole results (9). In consideration of the foregoing, we decided to attempt the Friedel-Crafts acylation of N-acetyl-9,10-dihydroacridine employing bromoacetyl bromide. The N-acetyl derivative was chosen in order to avoid any doubt regarding N acylation; and, aware of the possibility of nuclear halogenation, bromoacetyl bromide rather than acetyl chloride was used, so as to circumvent the bromination step to the bromo ketone.

As the first step in this work, a commercial grade of acridine was purified and reduced to 9,10-dihydroacridine in the presence of Raney nickel according to Adkins and Coonradt (10). The resulting acridane was smoothly N-acetylated in excellent yield by heating with acetyl chloride. The N-acetylation of 9,10-

dihydroacridine using acetic anhydride as the acylating agent was described recently (11). Our experimental work, however, was completed prior to the appearance of this paper. The aluminum chloride-catalyzed reaction of N-acetyl-9,10-dihydroacridine with bromoacetyl bromide in carbon disulfide proceeded without difficulty to give N-acetyl- ω -bromoacetyl-9,10-dihydroacridine in 50% yield (average of 6 runs). No attempt was made to work up the highly-colored, oily by-products, so it is not possible to say whether any isomeric bromo ketones were formed in the reaction. The condensation of the bromo ketone with secondary amines was effected in dry ether to give, in addition to amine hydrobromide, the corresponding amino ketones. With the exception of the tetrahydroisoquinolino analog, which was obtained crystalline, all of the amino ketones prepared were viscous syrups. Some difficulty was encountered in the catalytic hydrogenation² of the crude amino ketones, and it was found advantageous to purify them through their hydrochlorides before reduction. With the tetrahydroisoquinolino analog, catalytic hydrogenation of the amino ketone hydrochloride gave good results.

Because of the great tendency of 9,10-dihydroacridine (acridane) and its derivatives to revert to the parent, acridine ring system under mild oxidation conditions (*e.g.*, atmospheric oxygen), several of the amino alcohols described were deacetylated at the heterocyclic nitrogen function thereby regenerating the acridane structure. Conceivably, the 9,10 hydrogen atoms could be removed enzymatically (*in vivo*), thus enabling the true acridine system to act on the parasite. It is interesting to note that a slight increase in activity was observed with the des-N-acetyl amino carbinols (12).

The elucidation of the position occupied by the ω -bromoacetyl group is being deferred until adequate reference derivatives of acridine can be prepared by unambiguous syntheses. This phase of the problem will be reported in a future communication. Of the drugs prepared in this series, SN 6087 exhibited significant activity, while SN 5698 and SN 5849 were slightly active toward *P. Gallinaceum* (blood-inoculated chick infection) (12).

Acknowledgment. The microanalyses are by E. A. Garlock, Jr., formerly of this Laboratory.

EXPERIMENTAL

The melting points given are uncorrected.

9,10-Dihydroacridine. Crude acridine (Reilly) was purified through its dichromate as outlined by Graebe (13), although the final HCl treatment, described by him, was omitted. The acridine so obtained was dissolved in dry dioxane and digested with Raney nickel according to Adkins and Coonradt (*loc. cit.*). After a second reflux with nickel, the filtered dioxane solution was shaken at room temperature for 3 hrs. in the presence of fresh nickel and an initial hydrogen pressure of 100 atmospheres. Vacuum concentration (under nitro-

² Catalytic, rather than aluminum isopropoxide (Meerwein-Ponndorf-Verley), reduction of the amino ketones was chosen in order to circumvent the possibility of simultaneous hydrolysis of the N-acetyl group.

gen) of the filtered solution afforded reasonably pure 9,10-dihydroacridine (m.p. 169–70°). In this manner, working with 50–75 g. batches, 300 g. of crude acridine yielded 190 g. (69%) of 9,10-dihydroacridine which, in view of its air-sensitivity, was acetylated without further purification.

N-Acetyl-9,10-dihydroacridine. Ninety grams of 9,10-dihydroacridine was covered with 178 ml. (5 moles) of acetyl chloride (redistilled from freshly fused sodium acetate) and the mixture refluxed for 30 minutes on the steam-bath. The dark color which developed as the solid dissolved soon faded to a light yellow, and hydrogen chloride was evolved copiously. Treatment of the reaction mixture with ice gave a practically colorless, crystalline precipitate which was collected, well washed with water and air-dried. The yield of crude *N*-acetyl derivative was 110 g. Recrystallization from methanol afforded 96.5 g. (88%) of short, stout prisms; m.p. 149–151°. Three further recrystallizations raised the m.p. to 151.5–153°.

Anal. Calc'd for $C_{18}H_{13}NO$: C, 80.7; H, 5.87.

Found: C, 80.5; H, 6.07.

The Friedel-Crafts reaction: α -(ω -Bromoacetyl)-N-acetyl-9,10-dihydroacridine. Observing the usual precautions for the maintenance of anhydrous conditions, a stirred mixture of 65.2 g. (0.29 mole) of finely powdered *N*-acetyl-9,10-dihydroacridine and 65 g. (0.32 mole) of bromoacetyl bromide in 400 ml. of c.p. carbon disulfide was gradually treated, without cooling, during 1 hr. with 116 g. (0.87 mole) of powdered, anhydrous $AlCl_3$. Ten minutes after the initial addition of the latter, the reaction flask was immersed in a pan of warm water (55–60°) and heating continued as described below. Other than a slight, progressive darkening of the system during the early $AlCl_3$ additions, there was little sign of reaction. However, when approximately one-half of the catalyst had been added the reaction appeared to get under way, as evidenced by the evolution of HBr and the gradual separation of a light amber gum. Stirring and heating were maintained for 70 min. after the final $AlCl_3$ addition, and stirring continued for an additional 45 min. at room temp. After standing for an hour, the flask was cooled and the supernatant CS_2 decanted; it was practically devoid of reaction product. The gummy residue was decomposed by adding it, portion-wise to a stirred slurry of ice and 2 *N* HCl and the system thoroughly extracted with chloroform. Concentration (*vacuo*) of the water-washed and dried chloroform solution afforded a syrup which readily crystallized to a sticky, tan solid when rubbed with a little dry ether. After three triturations with small portions of ice-cold methanol, there remained 55 g. (55%) of practically colorless, crystalline powder, m.p. 155–158°. The bromo ketone crystallizes in small, six-sided plates from acetone, as well as from a benzene-petroleum ether (30–60°) mixture. After three recrystallizations from the latter, m.p. 161–163°.

Anal. Calc'd for $C_{17}H_{14}BrNO_2$: C, 59.3; H, 4.10; Br, 23.2.

Found: C, 59.5; H, 4.23; Br, 23.5.

α -(2-Diethylamino-1-hydroxyethyl)-N-acetyl-9,10-dihydroacridine hydrochloride (SN 6087). A mixture of 20 g. of *N*-acetyl- α -(ω -bromoacetyl) dihydroacridine and 9.4 g. (2.2 moles) of diethylamine in 250 ml. of dry ether was mechanically shaken for 15 hours. The resulting suspension was cooled (ice-water) and 8.7 g. of a mixture of diethylamine hydrobromide (8.3 g. or 93%) and a little unchanged bromo ketone (0.4 g.) was recovered. The water-washed and dried ethereal solution yielded, after concentration (*vacuo*), 17.6 g. of syrupy amino ketone. This was dissolved in 30 ml. of acetone and acidified with 10 ml. (excess) of 5.4 *N* alcoholic HCl . Addition of dry ether precipitated a light yellow gum which slowly became powdery when scratched. After decanting the supernatant solvent the hydrochloride was slurried with fresh, dry ether, filtered and dried in a vacuum desiccator; 19 g. (probably solvated). Because of the hygroscopic nature of the salt, no attempt was made to recrystallize it. Instead it was dissolved in cold water, basified (under ether) with 2 *N* NH_4OH and the regenerated amino ketone (14.1 g.) taken up in 170 ml. of methanol and hydrogenated in the presence of 0.25 g. of PtO_2 . Hydrogen absorption virtually ceased after 39 hrs. (0.88 mole absorbed). The syrupy amino alcohol (12.5 g.) in 30 ml. of acetone was cooled and acidified with 6.8 ml. (1 equiv.) of 5.4 *N* alcoholic HCl . Dilution with dry

ether precipitated a gum which solidified to a light yellow powder (13.9 g.) when scratched. The crude hydrochloride was dissolved in 500 ml. of boiling acetone, filtered and concentrated (*vacuo*) to ca. 50 ml.; crystallization was spontaneous, but slow. Overnight (5°) 4.5 g. of cream-colored prisms, m.p. 173–176°, separated. The mother liquor deposited another 1.8 g. of prisms (m.p. 175–177°) after 60 hrs. at 5°. Four recrystallizations from acetone gave the constant m.p. 180–182° d.

Anal. Calc'd for $C_{21}H_{27}ClN_2O_2$: C, 67.3; H, 7.25.

Found: C, 67.1; H, 7.35.

The combined mother liquors on concentration and keeping yielded about 1 g. of impure, crystalline hydrochloride. The remaining oil could not be crystallized.

x-(2-Diethylamino-1-hydroxyethyl)-9,10-dihydroacridine (SN 5971). A suspension of 13 g. of the above, powdery amino alcohol hydrochloride (not crystallized) was heated with 200 ml. of 5% alcoholic KOH for 15 min. on the steam-bath. The clear, yellow solution was poured into 1 liter of 5% aqueous NaCl and thoroughly extracted with ether. The latter, after several washings with 5% NaCl, was dried and concentrated (*vacuo*, under N_2) to give a syrup which slowly crystallized after one-half hour of alternate scratching and standing. Two recrystallizations from 70% ethanol afforded 5.5 g. of nearly colorless needles, m.p. 107–108.5°. An analytical sample, after three more recrystallizations, showed the m.p. 108–110°. The substance, as might be inferred from its structural relationship to dihydroacridine, is air-sensitive and turns brown after exposures of short duration (36–48 hrs.).

Anal. Calc'd for $C_{19}H_{24}N_2O$: C, 77.0; H, 8.16.

Found: C, 76.4; H, 8.17.

x-(2-Dimethylamino-1-hydroxyethyl)-*N*-acetyl-9,10-dihydroacridine hydrochloride (SN 5981). To an ice-cooled solution of 12 g. (6 moles) of dimethylamine in 250 ml. of dry ether was added 15 g. of finely powdered bromo ketone. The flask was intermittently cooled and shaken for 10 min., mechanically shaken for 5 hrs. then kept at 5° overnight. After removing dimethylamine hydrobromide (5.2 g. or 92%), the washed and dried ethereal solution gave 11.9 g. of the syrupy amino ketone. A solution of the latter in 20 ml. acetone was acidified with 9 ml. of 15% alcoholic HCl and strongly diluted with dry ether. Scratching caused the separation of the powdery hydrochloride. This was triturated twice with dry ether and the amino ketone regenerated under ether (NH_4OH). The resulting clear, amber syrup (10 g.) in 50 ml. of methanol, with 0.25 g. PtO_2 , absorbed 1.05 moles of hydrogen (48 hrs.). The filtered methanol solution yielded 8.9 g. of syrupy amino alcohol. A solution of the latter in 20 ml. of acetone afforded, after acidification with 7 ml. of 15% alcoholic HCl and dilution with dry ether, 10 g. of a cream-colored, micro-crystalline powder which was dissolved in 1 liter of boiling acetone (containing a few drops of methanol) and clarified with Norit. Overnight (20°) the solution deposited 3.5 g. (crop I) of pale yellow crystals. Another 2 g. (crop II) of crystalline hydrochloride was derived from the concentrated mother liquor (60 hrs. at 20°). The salt crystallizes from acetone (containing a few drops of methanol) in clusters of 4-sided plates which are obviously solvated, m.p. 124–127° (foams). The m.p. was not changed appreciably on recrystallization. That the salt is solvated (methanol) is evident from the analytical data, but an accurate methanol determination could not be obtained owing to mechanical losses caused by frothing during vacuum drying.

Anal. Calc'd for $C_{19}H_{23}ClN_2O_2 \cdot CH_3OH$: C, 63.4; H, 7.18.

Found: C, 63.4; H, 7.01.

x-(2-Dimethylamino-1-hydroxyethyl)-9,10-dihydroacridine (SN 6779). This substance was prepared from the above-described *N*-acetyl amino alcohol hydrochloride by hydrolysis with ethanolic KOH as outlined under the diethylamino homolog. From 7.5 g. of crude hydrochloride 3.3 g. of deacetylated base resulted, which crystallized in needles from 70% ethanol; m.p. 120–121.5°. The base is air-sensitive.

Anal. Calc'd for $C_{17}H_{23}N_2O$: C, 76.1; H, 7.51.

Found: C, 76.6; H, 7.48.

x-(2-Di-*n*-propylamino-1-hydroxyethyl)-*N*-acetyl-9,10-dihydroacridine hydrochloride (SN 5928). This member of the series was synthesized in the same manner as the diethylamino

homolog. From 10 g. of bromo ketone and 5.9 g. (2 moles) of di-*n*-propylamine in 150 ml. of dry ether, the following were obtained in the order given: 11 g. of syrupy amino ketone; 10 g. of crude, amino ketone hydrochloride and 8.2 g. of regenerated amino ketone base. The latter, in 100 ml. of methanol with 0.35 g. PtO_2 , absorbed 0.93 mole of hydrogen in 60 hrs. Conversion of the syrupy amino alcohol to its hydrochloride was accomplished in acetone with alcoholic HCl and dry ether. The crude salt (6.9 g.) was recrystallized from acetone-ether; after 48 hrs., 4.2 g. of small, colorless prisms of m.p. $186\text{--}188^\circ \text{d}$. Two additional recrystallizations raised the m.p. to $190\text{--}191.5^\circ \text{d}$.

Anal. Calc'd for $\text{C}_{23}\text{H}_{31}\text{ClN}_2\text{O}_2$: C, 68.5; H, 7.76.

Found: C, 68.4; H, 7.84.

x-(2-Di-*n*-propylamino-1-hydroxyethyl)-9,10-dihydroacridine (SN 5698). Alkaline hydrolysis (5% ethanolic KOH) of 8 g. of the above amino alcohol hydrochloride resulted in a syrup which slowly crystallized when scratched. Recrystallization from 70% ethanol gave 4.1 g. of air-sensitive, felted needles, m.p. $91\text{--}93^\circ$. After three recrystallizations, the m.p. was $92\text{--}94^\circ$.

Anal. Calc'd for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}$: C, 77.7; H, 8.70.

Found: C, 77.6; H, 9.13.

x-(2-Di-*n*-butylamino-1-hydroxyethyl)-*N*-acetyl-9,10-dihydroacridine hydrochloride (SN 5934). Employing the procedure outlined above for the diethylamino compound, the condensation of 15 g. of bromo ketone with 11.3 g. (2 moles) of di-*n*-butylamine in 200 ml. of dry ether gave, in the order named: 15.4 g. of syrupy amino ketone base; 12.3 g. of crude amino ketone hydrochloride and 9 g. of regenerated amino ketone. Catalytic reduction of the latter in 100 ml. of methanol with 0.35 g. PtO_2 (1.1 moles of H_2 absorbed in 60 hrs.) gave 8.5 g. of an amber syrup. This was taken up in 25 ml. of acetone and treated with 4 ml. (1 equivalent) of 5.4 *N* alcoholic HCl . The addition of dry ether precipitated the hydrochloride as a yellow gum which gradually solidified when scratched. The crude salt (7.8 g.) was dissolved in boiling acetone, filtered, concentrated to small volume and treated with dry ether to light turbidity. After 36 hrs. 3.8 g. of clusters of practically colorless prisms separated; m.p. $178\text{--}180^\circ \text{d}$. Three crystallizations (acetone-ether) gave the constant m.p. $183\text{--}184.5^\circ \text{d}$.

Anal. Calc'd for $\text{C}_{25}\text{H}_{35}\text{ClN}_2\text{O}_2$: C, 69.7; H, 8.19.

Found: C, 69.4; H, 8.29.

Another 0.8 g. of less pure hydrochloride was recovered from the mother liquors.

x-(2-Di-*n*-amylamino-1-hydroxyethyl)-9,10-dihydroacridine (SN 5849). To a cooled suspension of 20 g. of bromo ketone in 250 ml. of dry ether, 18.3 g. (2 moles) of di-*n*-amylamine was added and the system mechanically shaken for 15 hrs. After chilling in ice, 12.5 g. of di-*n*-amylamine hydrobromide was removed. The ethereal solution afforded 22.5 g. of amino ketone base which, in turn, gave an oily hydrochloride when treated in cold acetone, with the calculated amount of alcoholic HCl . The hydrochloride remained gummy despite repeated triturations with fresh portions of dry ether and scratching. The regenerated amino ketone 13.5 g. (NH_4OH -ether) was reduced in 60 ml. of methanol in the presence of 0.6 g. PtO_2 (0.91 mole H_2 absorbed in 62 hrs.). The hydrochloride of the resulting amino alcohol, formed in acetone with alcoholic HCl and dry ether, appeared as a gum which could not be crystallized. The amino alcohol base was therefore deacetylated directly.

Deacetylation. Hydrolysis of 11.9 g. of the above base in 180 ml. of 5% alcoholic KOH , as described previously, afforded 7.5 g. of a syrup which slowly crystallized (2 hrs.). Recrystallization from 70% ethanol gave 6 g. of practically colorless, air-sensitive needles. The melting point, after three crystallizations, was $78\text{--}80^\circ$.

Anal. Calc'd for $\text{C}_{25}\text{H}_{35}\text{N}_2\text{O}$: C, 78.9; H, 9.54.

Found: C, 78.5; H, 9.51.

x-(2-Tetrahydroisoquinolino-1-oxoethyl)-*N*-acetyl-9,10-dihydroacridine. The condensation of 9 g. of bromo ketone with 6.95 g. (2 moles) of tetrahydroisoquinoline (14) in 150 ml. of dry ether gave, after 15 hrs. shaking, 14.3 g. of a colorless precipitate which proved to be a mixture consisting of a small amount of unchanged tetrahydroisoquinoline, the hydro-

bromide of the latter, and the expected amino ketone. Two triturations of the mixture with dry ether removed tetrahydroisoquinoline; the amine hydrobromide was extracted by repeated leaching with warm (40°) water. The residual, water-insoluble amino ketone was a colorless powder, 8.6 g. (84%) which crystallized from acetone-water in diamond-shaped prisms. After three crystallizations, the m.p. was 162–164.5°.

Anal. Calc'd for $C_{18}H_{24}N_2O_2$: C, 78.7; H, 6.10.

Found: C, 78.4; H, 6.30.

x-(2-Tetrahydroisoquinolino-1-hydroxyethyl)-N-acetyl-9,10-dihydroacridine hydrochloride (SN 6088). A solution of 6.2 g. of the above amino ketone in 60 ml. acetone was treated with 2.85 ml. (1 equiv.) of 5.4 N ethanolic HCl and the powdery hydrochloride precipitated with dry ether (6.9 g.). The salt, in 130 ml. of methanol, was digested with Norit for a few minutes and, after filtration, reduced in the presence of 0.35 g. of PtO_2 (1.05 moles H_2 absorbed in 26 hrs.). The syrupy residue, from concentration (*vacuo*) of the filtered solution, was taken up in a little acetone and strongly diluted with dry ether. The amino alcohol hydrochloride separated as a gum which quickly solidified when scratched. After a second trituration with dry ether, the pale yellow powder (5.9 g.) was dissolved in boiling acetone, to which a few drops of methanol were added, digested with Norit, filtered and concentrated to small volume. The hydrochloride crystallized spontaneously; 3.5 g. of nearly colorless, crystalline crusts. The constant m.p. 216–217° d. was obtained after three recrystallizations (acetone-ether).

Anal. Calc'd for $C_{28}H_{37}ClN_2O_2$: C, 71.8; H, 6.26.

Found: C, 71.4; H, 5.94.

x-(2-Transdecahydroquinolino-1-hydroxyethyl)-N-acetyl-9,10-dihydroacridine hydrochloride (SN 6089). Ten grams of bromo ketone shaken with 8.1 g. (2 moles) of transdecahydroquinoline (15) in 150 ml. of dry ether (15 hrs.) afforded the following intermediates: 11.2 g. of syrupy amino ketone; 11.3 g. of crude amino ketone hydrochloride, and 9.1 g. of regenerated amino ketone base. The latter in 100 ml. of methanol, in the presence of 0.3 g. PtO_2 , absorbed 1 mole of H_2 (39 hrs.) to give 8.7 g. of oily amino alcohol. A solution of this in 25 ml. of acetone was treated with 4.1 ml. (1 equiv.) of 5.4 N ethanolic HCl and the hydrochloride precipitated as a gum with dry ether. Trituration with fresh, dry ether gave a pale-yellow powder (9.4 g.). This was dissolved in 300 ml. of boiling acetone (Norit) filtered and concentrated (*vacuo*). After 24 hrs. (20°), 6.4 g. of a colorless, microcrystalline powder was collected. Repeated recrystallization from acetone gave colorless, crystalline crusts, m.p. 175–177° d.

Anal. Calc'd for $C_{28}H_{37}ClN_2O_2$: C, 70.8; H, 7.54.

Found: C, 70.6; H, 7.82.

x-(2-Transdecahydroquinolino-1-hydroxyethyl)-9,10-dihydroacridine hydrochloride (SN 5929). A solution of 4.3 g. of the above amino alcohol hydrochloride in 55 ml. of 5% ethanolic KOH was heated for 2 hrs. (steam-bath) then poured into 500 ml. of 15% NaCl solution. The light-tan precipitate was collected, trituated 3 times with water and dried in a vacuum desiccator—yield 3 g. A filtered solution of the latter in 125 ml. of warm, absol. ethanol was acidified with 1.8 ml. (1 equiv.) of 5.4 N ethanolic HCl. After 24 hrs. (5°), the hydrochloride was obtained as virtually colorless, micro-needles, 2.7 g. Three recrystallizations from absol. ethanol-ether gave the constant m.p. 232–234° d.

Anal. Calc'd for $C_{28}H_{31}ClN_2O$: C, 72.3; H, 7.83.

Found: C, 72.0; H, 7.86.

SUMMARY

The aluminum chloride-catalyzed bromoacetylation of N-acetyl-9,10-dihydroacridine is described.

Several new amino carbinols derived from *x*-(ω -bromoacetyl)N-acetyl-9,10-dihydroacridine have been prepared.

The plasmodicidal activity of three members of this series of drugs has been noted.

BETHESDA 14, MARYLAND.

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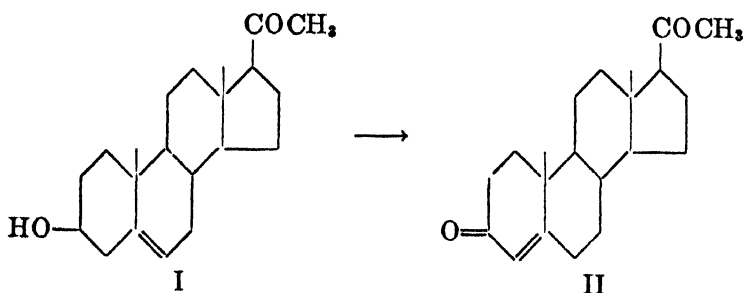
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RANEY NICKEL AS AN ORGANIC OXIDATION-REDUCTION CATALYST¹

E. C. KLEIDERER AND E. C. KORNFELD

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The versatility of Raney nickel as a catalyst in effecting various reductive transformations of organic compounds is quite well known (1, 2). Catalytic oxidations in the presence of Raney nickel, however, are relatively obscure (2, 11). Paul (3) and Palfrey (4), for example, have shown that certain secondary alcohols may be dehydrogenated catalytically to the corresponding ketones; however, temperatures up to 250° must be used, and even then yields leave much to be desired. A recent report (5) of work by H. Ruschig at the I. G. Farbenindustrie laboratories has described the catalytic conversion of pregnenolone (I) to pro-



gesterone (II) in the presence of a special Raney nickel catalyst and cyclohexanone as a hydrogen acceptor. The object of the present investigation was to determine the generality of this oxidation and to study the possibility of using it in the reverse sense; *i.e.*, as a reductive method in the presence of a hydrogen donor. The latter phase would constitute an extension of the work of Mozingo *et al.* (12).

Preliminary attempts to oxidize cholesterol to cholestenone using cyclohexanone as hydrogen acceptor showed that the special aerated Raney nickel as prepared by Ruschig (5) was considerably less effective than the usual Raney nickel kept under toluene. For this reason ordinary Raney nickel was employed in all the subsequent investigations. Cyclohexanone was used as hydrogen acceptor in the oxidations because of its favorable oxidation potential (6), and the method involved merely refluxing a mixture of the compound to be oxidized, with the hydrogen acceptor, and catalyst in toluene. Table I shows the variety of secondary alcohols which may be converted to the corresponding ketones by this procedure. The oxidation of cholesterol involves a simultaneous shift of the Δ^5 double bond to the Δ^4 position in conjugation with the carbonyl group. This shift occurs likewise in the usual Oppenauer oxidation of cholesterol (7).

¹ Since the completion of this work, related conversions by means of Raney nickel have been reported by Dubois (15).

When the redox reaction was next studied as a preparative reduction method, it was found that a wide variety of compounds could be reduced in the presence of any of several different potential hydrogen donors (see Table II). The types of conversion effected are similar to those brought about either by high pressure hydrogenation (1) or by the action of alkali on nickel-aluminum alloy (9). Carbonyl groups, activated ethylenic, and acetylenic bonds in varied environments are smoothly reduced. Hydrogenolysis of the carbon-oxygen bond occurs when α to an aromatic ring. Related reductions have been carried out by Bougault (11) and by Mozingo (12) with Raney nickel, the latter using ethanol as solvent. These workers believed that the hydrogen for reduction was supplied only by the catalyst and have not mentioned the possibility that the hydroxylic solvents employed may act as hydrogen donors. Support for this latter view has been

TABLE I
OXIDATIONS*

COMPOUND OXIDIZED	HYDROGEN ACCEPTOR	CATALYST, G./G. CPD.	HOURS REFLUX	PRODUCT ISOLATED	% YIELD
Cholesterol	Cyclohexanone	2.0	24	Cholestenone	80
Benzoin	"	2.0	24	Benzil	35
Benzhydrol	"	2.0	22	Benzophenone	30
Dihydrocholesterol	"	2.5	24	Cholestanone	80
Epicoprostanol (8)	"	1.5	24	Coprostanone	50
Fluorenol	"	2.5	24	Fluorenone	76

* Under the conditions of the oxidation xanthydrol gave a 30% yield of dixanthyl, m.p. 207-208°. This seems to be an anomalous case.

Anal. Calc'd for $C_{28}H_{48}O_2$: C, 86.16; H, 5.01.

Found: C, 85.96; H, 4.97.

obtained in the isolation of acetone (as its 2,4-dinitrophenylhydrazone) from reduction experiments in which isopropanol was used as hydrogen donor. Under similar conditions Wolfrom (13) has recently isolated acetaldehyde when using ethanol as solvent. It is thus probable that both the hydrogen donor and the hydrogen adsorbed on the catalyst play a part in these reductions, especially when only small amounts of catalyst are used. We have found, however, that in the presence of excess Raney nickel, stilbene may be reduced in 80% yield to dibenzyl when dioxane is used as solvent. It is evident, therefore, that reductions may be effected entirely by means of the hydrogen adsorbed on the catalyst. The rôle of the hydrogen donor solvents is thus an accessory one.

The identity of each product formed in the oxidations or reductions was established either by mixed melting point determinations with authentic samples or by analysis. The tables are largely self-explanatory.

EXPERIMENTAL

Preparation of the nickel catalyst. Raney nickel was prepared by the method of Mozingo (14), and after the exhaustive washing the water was decanted and toluene added. The

TABLE II
REDUCTIONS

COMPOUND REDUCED	HYDROGEN DONOR	CATALYST, G./G. CPD.	HOURS REFLUX	PRODUCT ISOLATED	% YIELD
Cholestanone	Cyclohexanol	2.0	22	Dihydrocholesterol	50
Coprostanone	"	2.0	22	Epicoprostanol	20
Benzoin	"	2.5	24	Dibenzyl ^a	58
Desoxybenzoin	"	2.5	24	"	20
Cholestenone	"	1.7	24	Dihydrocholesterol	10
Mesohydrobenzoin	"	1.6	24	Dibenzyl	17
Benzophenone	Diethylcarbinol	2.5	24	Diphenylmethane ^b	75
"	Isopropanol	3.0	31	"	36
Desoxyanisoin	Cyclohexanol	1.1	24	<i>p,p'</i> -Dimethoxydi- benzyl ^c	80
Anisal- <i>p</i> -methoxy- acetophenone	Diethylcarbinol	3.2	24	1,3-Di- <i>p</i> -methoxy- phenylpropane ^d	80
Stilbene	"	3.4	24	Dibenzyl	60
Benzilic acid	Isopropanol	4.6	16	Diphenylmethane ^e	5
Laurone	"	2.5	23	Diundecylcarbinol	80
Ethyl <i>o</i> -benzoyl- benzoate	"	3.2	19	<i>o</i> -Benzylbenzoic acid ^f	86
Diphenylacetylene	Ethanol	6.5	7	Dibenzyl	77
Di-[4,4'-tetra- methyldiamino- benzhydryl] ether	Isopropanol	4.8	16	4,4'-Tetramethyldi- aminodiphenyl- methane	50
3-Acetylquinoline	"	5	24	3-Ethyl-5,6,7,8- tetrahydroquino- line ^g	62
9-Anthraldehyde	"	4	6	9-Hydroxymethyl- anthracene ^h + anthracene	10 10

^a Anal. Calc'd for C₁₄H₁₄: C, 92.26; H, 7.74.

Found: C, 91.83; H, 7.88.

^b Tetranitro derivative m.p. 170–172°.

^c Anal. Calc'd for C₁₈H₁₈O₂: C, 79.31; H, 7.49.

Found: C, 78.63; H, 7.14.

^d Anal. Calc'd for C₁₇H₂₀O₂: C, 79.65; H, 7.86.

Found: C, 79.48; H, 7.62.

^e Most of the benzilic acid was recovered unchanged. The method of Schwenk and Papa (9) is superior for acidic compounds.

^f Obtained by alkaline hydrolysis of the crude reduction product.

^g Isolated as the picrate, m.p. 160–161.5° (10).

Anal. Calc'd for C₁₁H₁₁N·C₆H₅O₇N₃: C, 52.31; H, 4.65.

Found: C, 52.41; H, 4.45.

^h Anal. Calc'd for C₁₈H₁₂O: C, 86.50; H, 5.81.

Found: C, 86.92; H, 5.66.

toluene was then distilled until no further water was removed. The catalyst was stored under toluene.

Typical oxidation procedure. Oxidation of dihydrocholesterol. Toluene (150 ml.), cyclohexanone (50 ml.), Raney nickel (10 to 15 g.), and dihydrocholesterol (5 g.) were refluxed

with efficient stirring for 24 hours. The catalyst was filtered, and the toluene and cyclohexanone were removed by distillation *in vacuo*. The residue was taken up in ether, filtered, and the ether removed on a steam-bath. The product was recrystallized from ethanol, m.p. 127–129°; yield, 80%. Other oxidations were run in an exactly similar fashion.

Typical reduction procedure. Reduction of anisal-p-methoxyacetophenone. Toluene (125 ml.), diethylcarbinol (75 ml.), Raney nickel (15–16 g.), and anisal-p-methoxyacetophenone (5 g.) were refluxed with stirring for 24 hours. The catalyst was filtered, and the solvents were distilled *in vacuo*. The product was recrystallized from ethanol, m.p. 42–44°; yield, 80%. Further recrystallization raised the melting point to 45.0–45.5°. Reductions using cyclohexanol and diethylcarbinol as hydrogen donors were run exactly as this example except that digitonin precipitation was used to separate mixtures formed in reactions (2) and (5) (Table II). In those cases in which isopropanol or ethanol were used, toluene was omitted, and in its place extra donor solvent was substituted.

Reduction in absence of donor solvent. Reduction of stilbene. A mixture of stilbene (5 g.), dioxane (200 ml.), and Raney nickel (22 g.) was refluxed with stirring for 24 hours. The catalyst was filtered, and the filtrate was concentrated *in vacuo*. The product was recrystallized from methanol. Dibenzyl was thus obtained in 80% yield, m.p. 52.0–52.5°.

SUMMARY

1. Raney nickel in the presence of a hydrogen acceptor may be used to catalyze the oxidation of secondary alcohols to the corresponding ketones.

2. Reduction of the carbonyl group, ethylenic double bond, and acetylenic triple bond may likewise be effected by Raney nickel in the presence of a hydrogen donor. Hydrogenolysis of carbon-oxygen bonds α to aromatic nuclei has been observed.

INDIANAPOLIS, INDIANA

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SOME REACTIONS OF AMIDONE

EVERETTE L. MAY AND ERICH MOSETTIG

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This project was undertaken in order to study a number of transformations of the amidone (6-dimethylamino-4,4-diphenyl-3-heptanone) (1, 2) molecule (V) and to observe the pharmacological changes induced by such transformations.

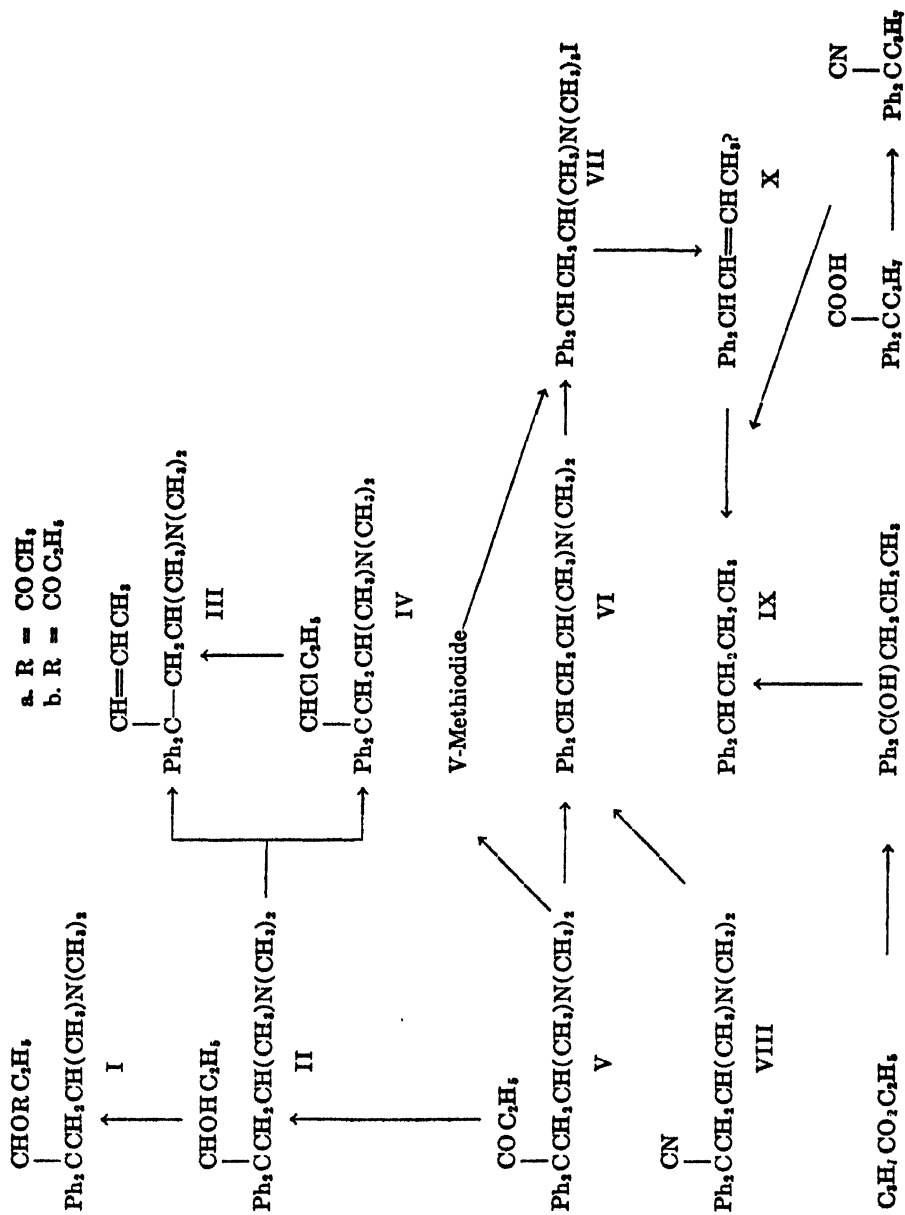
The carbonyl group of V was found to be relatively unreactive. It did not give a semicarbazone under the usual conditions and resisted reduction with aluminum isopropoxide or sodium amalgam. It was unaffected when subjected to hydrogenation with Raney nickel at room temperature and atmospheric pressure. With platinum oxide, however, the corresponding carbinol (II) was formed in a yield of 80%; only one of the two possible diastereoisomers was isolated. Acetylation of II with acetic anhydride and pyridine gave a 40% yield of the O-acetyl derivative (I-a). By the method of Houben (3) (acid anhydride, ethylmagnesium bromide) I was obtained in yields of 80-90%.

By the action of thionyl chloride II was converted, under mild conditions, to a mixture of 3-chloro-6-dimethylamino-4,4-diphenylheptane (IV) (40% yield) and 6-dimethylamino-4,4-diphenylheptene-2 (III) (20% yield). When the reaction was carried out in boiling benzene, the yield of IV was about 10% and that of III 30-40%. Results similar to the latter were obtained with II and phosphorus pentachloride in chloroform. Finally III was formed in yields of 30-40% on treatment of II with phosphorus pentoxide in boiling toluene, and in the reaction of II or IV with hydriodic acid and phosphorus in boiling acetic acid. Efforts to hydrogenate III and IV under a wide variety of conditions gave erratic results. Hydrogen absorption either did not proceed at all, or else showed no tendency to cease at any definite molar stage. No crystalline, homogeneous reduction products could be isolated from the resulting mixtures.

Amidone was not attacked in the Clemmensen reduction. When it was subjected to the Wolff-Kishner reaction as modified by Huang-Minlon (4), a product was obtained which, on the basis of carbon-hydrogen analysis of three of its salts,¹ appeared to be isomeric with V. However, on degradation of this product it became obvious that it was 3-dimethylamino-1,1-diphenylbutane (VI), formed by alkaline cleavage of the ethyl keto group. Omission of the hydrazine did not alter the course of the reaction, while omission of both the hydrazine and the alkali led to extensive decomposition of V. Essentially no reaction took place when V and concentrated hydrochloric acid were heated together at 200°.

Hofmann degradation of the methiodide of VI (which was formed also by alkali treatment of the methiodide of V) and hydrogenation of the resulting olefin (X) gave 1,1-diphenylbutane (IX). This hydrocarbon was obtained in low

¹ Hydrochloride. Calc'd for $C_{21}H_{28}ClNO$: C, 72.9; H, 8.2. Found: C, 73.2; H, 8.2. Picrate. Calc'd for $C_{27}H_{30}N_4O_8$: C, 60.2; H, 5.6. Found: C, 60.3; H, 5.4. Perchlorate. Calc'd for $C_{21}H_{28}ClNO_4$: C, 61.5; H, 6.9. Found: C, 61.3; H, 6.8.



yield, along with α,α -diphenylvaleric acid by alkali treatment of α,α -diphenylvaleronitrile, and was synthesized in an over-all yield of 50% from ethyl butyrate via 1,1-diphenyl-1-butanol. The latter in acetic acid² containing traces of perchloric acid was hydrogenated to IX with palladium-charcoal or palladium-barium sulfate catalyst. The 1,1-diphenylbutane was characterized through its solid dinitro derivative. The cleavage product VI could also be obtained in good yield by the action of alkali on 4-dimethylamino-2,2-diphenylpentanenitrile. No intermediate acid was isolated in this instance.

Conversion of amidone to the corresponding carbinol (II) results in a marked reduction of morphine-like characteristics including analgesic effect. Activity is restored practically to that of amidone by acetylation of the hydroxyl group of II and to a lesser extent by propionylation. Replacement of the hydroxyl group by chlorine gives a nearly inactive compound (IV). The olefinic compound III approximates II in activity, while the scission product VI is inactive (Nathan B. Eddy) (5).

Acknowledgment. Microanalyses are from the Institute analytical service laboratory under the direction of C. A. Kinser.

EXPERIMENTAL³

6-Dimethylamino-4,4-diphenyl-3-heptanol (II). A mixture of 10 g. of V hydrochloride, 0.4 g. of platinum oxide, and 50 cc. of methanol absorbed one mole of hydrogen during twelve to twenty-four hours. To the filtered solution was added 7 cc. of concentrated ammonium hydroxide and 15 cc. of water, with warming. Upon gradual cooling, finally in ice, 7.3 g. (80%) of II, m.p. 100–101° separated; prisms from aqueous methanol, m.p. 100–100.5°. V base could be hydrogenated with equal facility.

Anal. Calc'd for $C_{21}H_{25}NO$: C, 80.9; H, 9.4.

Found: C, 81.1; H, 9.4.

The hydrochloride, isolated directly from the reduction mixture or prepared from the base with alcoholic hydrogen chloride, crystallized from methanol-ether in prisms of m.p. 190–193° and 200–203°.

Anal. Calc'd for $C_{21}H_{25}ClNO$: C, 72.5; H, 8.7.

Found: C, 72.6; H, 8.6.

3-Acetoxy-6-dimethylamino-4,4-diphenylheptane (I-a) hydrochloride. To a stirred, ice-cooled solution of 1.5 g. of II in 20 cc. of dry ether was added 10 cc. of 1 M ethylmagnesium bromide, then 1.3 cc. of acetic anhydride in 20 cc. of dry ether. The mixture was refluxed for one-half hour, shaken overnight, and poured into ice-cold, dilute alkali. The ether was dried and acidified with 15% alcoholic hydrogen chloride to give 1.7 g. (90%) of product melting at 207–209°; prisms from methanol-ether.

Anal. Calc'd for $C_{23}H_{27}ClNO_2$: C, 70.8; H, 8.3.

Found: C, 70.5; H, 8.3.

6-Dimethylamino-4,4-diphenyl-3-propionyloxyheptane (I-b) hydrochloride. This compound, prepared similarly to I-a in a yield of 80%, crystallized from acetone-ether in rosettes, m.p. 182–184°.

Anal. Calc'd for $C_{24}H_{29}ClNO_2$: C, 71.4; H, 8.5.

Found: C, 71.4; H, 8.3.

² When methanol was used in lieu of acetic acid, absorption did not stop at one mole.

³ All melting and boiling points are uncorrected.

⁴ This material was generously supplied by the Mallinckrodt Chemical Works and Merck & Co., Inc.

The picrate crystallized from ethanol in yellow prisms of m.p. 168–169°.

Anal. Calc'd for $C_{10}H_{12}N_4O_9$: C, 60.4; H, 6.1.

Found: C, 60.6; H, 6.0.

Reaction of II with thionyl chloride. (a) *3-Chloro-6-dimethylamino-4,4-diphenylheptane* (IV). To a stirred solution of 5 g. of II in 20 cc. of dry benzene was added during five minutes (temperature 15–25°) 1.5 cc. of thionyl chloride. After standing for one hour at room temperature, the solution was diluted with 60 cc. of dry ether to give, on cooling at 5° overnight, 2.4 g. (40%) of IV hydrochloride, m.p. 113–117°. It was converted to the base (aqueous ammonia) which, after drying in ether, crystallized to a solid of m.p. 84–87°; needles from ligroin (b.p. 30–60°), m.p. 88–89.5°.

Anal. Calc'd for $C_{21}H_{28}ClN$: C, 76.5; H, 8.5.

Found: C, 76.8; H, 8.3.

The hydrochloride, prepared from the base in acetone-ether with hydrogen chloride gas, crystallized in clusters of needles of m.p. 120–121° (gas evolution).

Anal. Calc'd for $C_{21}H_{28}Cl_2N$: C, 68.8; H, 8.0.

Found: C, 68.6; H, 7.7.

Crystallization of this hydrochloride from methanol-ether gave prisms of m.p. 123–124° (gas evolution). Carbon-hydrogen analysis indicated one mole of solvate methanol which was indeterminate by loss in weight *in vacuo* at 98°.

Anal. Calc'd for $C_{21}H_{28}Cl_2N \cdot CH_3OH$: C, 66.3; H, 8.3.

Found: C, 66.6; H, 8.2.

The picrate, prepared from the base or either hydrochloride with aqueous alcoholic picric acid, crystallized from aqueous ethanol in yellow needles of m.p. 134.5–135°.

Anal. Calc'd for $C_{27}H_{31}ClN_4O_7$: C, 58.0; H, 5.6.

Found: C, 58.3; H, 5.5.

(b) *6-Dimethylamino-4,4-diphenylheptene-2* (III). The filtrate from the 2.4 g. of IV hydrochloride was shaken with an excess of aqueous ammonia, dried over sodium sulfate, and acidified with hydrogen chloride gas. The resulting oil was cooled, washed with dry ether, and crystallized from ethyl acetate-ether to give 1.1 g. (18%) of a dihydrochloride^a of III, m.p. 87–89°. It was converted to the base (aqueous ammonia-ether) which was distilled at 0.05 mm. (bath temperature 120–125°) to give a colorless, mobile oil.

Anal. Calc'd for $C_{21}H_{27}N$: C, 86.0; H, 9.3.

Found: C, 86.3; H, 9.4.

The hydrochloride, prepared by addition of one mole of hydrogen chloride to an acetone solution of the base followed by dilution with ether, or as described in footnote 5, crystallized from ethyl acetate in rectangular prisms, m.p. 133–135°, after drying in a vacuum desiccator (hygroscopic).

Anal. Calc'd for $C_{21}H_{28}ClN$: C, 76.4; H, 8.6.

Found: C, 75.8; H, 8.6.

The picrate, prepared from the base or either hydrochloride with aqueous ethanolic picric acid, melted at 112–114°; yellow prisms.

Anal. Calc'd for $C_{27}H_{30}N_4O_7$: C, 62.1; H, 5.8.

Found: C, 62.0; H, 5.8.

Reaction of II with thionyl chloride in boiling benzene. A mixture of 3.0 g. of II, 1.5 cc. of thionyl chloride and 12 cc. of dry benzene was refluxed for one-half hour and partitioned between ether and aqueous ammonia. The dried ether layer was neutralized with 1.5 g. of about 17% alcoholic hydrogen chloride and diluted with ligroin (b.p. 30–60°) to give, after seeding and cooling for two days (finally at 5°), 1.1 g. of the hydrochloride of III, m.p. 131–133°. The filtrate deposited 0.3 g. of the hydrochloride of IV, m.p. 117–119°.

^a *Anal.* Calc'd for $C_{21}H_{27}N \cdot 2HCl$: C, 68.8; H, 8.0; HCl (one mole), 9.96. Found: C, 69.6; H, 8.1; loss in wt. (77°, high vacuum), 8.71. This dihydrochloride is unstable and is converted to the monohydrochloride by evaporating its methanol solution to dryness and recrystallizing the residue from ethyl acetate.

Reaction of II with phosphorus pentachloride and with phosphorus pentoxide. To a stirred mixture of 5.0 g. of phosphorus pentachloride and 40 cc. of dry chloroform was added 3.5 g. of II in 20 cc. of chloroform during twenty minutes. The mixture was allowed to stand overnight, evaporated to dryness *in vacuo*, and the residue treated with cold, dilute sodium carbonate and ether. The ether was dried and acidified with hydrogen chloride to give a semisolid which crystallized from acetone-ether, yielding 1.0 g. of the dihydrochloride of III (*cf.* footnote 5), m.p. 85–90°. II (1.0 g.), 1.0 g. of phosphorus pentoxide and 5 cc. of dry toluene, refluxed for two hours, gave 0.4 g. of the dihydrochloride of III, m.p. 86–89°.

Reaction of II and of IV with hydriodic acid and phosphorus. II (1.0 g.), 2 cc. of 57% hydriodic acid, 0.4 g. of red phosphorus, and 5 cc. of acetic acid, refluxed for three hours, filtered, the filtrate evaporated to dryness, and the residue partitioned between 5% sodium hydroxide and ether, gave as described above, 0.3 g. of an unidentified fraction of needles and 0.3 g. of the dihydrochloride of III.

Similarly (reaction time one hour) 0.5 g. of IV gave 0.2 g. of III dihydrochloride.

3-Dimethylamino-1,1-diphenylbutane (VI) picrate. (a) *From V.* A mixture of 4 g. of V, 3.2 g. of potassium hydroxide, and 20 cc. of triethylene glycol was refluxed (bath temperature 220–230°) for four hours, diluted with water and ether, and the ether layer evaporated. To the residue was added 4 g. of picric acid in alcohol and the mixture heated to solution to give, on dilution with water and cooling, 5.4 g. (90%) of VI picrate, m.p. 138–140°. It crystallized from ethanol in yellow plates, of m.p. 138–139°.

Anal. Calc'd for $C_{24}H_{28}N_4O_7$: C, 59.7; H, 5.4.

Found: C, 60.0; H, 5.5.

The perchlorate crystallized from absolute ethanol in rods, m.p. 158–159°.

Anal. Calc'd for $C_{18}H_{24}ClNO_4$: C, 61.1; H, 6.8.

Found: C, 61.3; H, 6.8.

The hydrochloride, m.p. 151–155°, crystallized from ethyl acetate in prisms.

Anal. Calc'd for $C_{18}H_{24}ClN \cdot 0.5H_2O$: C, 72.4; H, 8.4.

Found: C, 73.2; H, 8.2.

(b) *From 4-dimethylamino-2,2-diphenylpentanenitrile.* As described under (a) 1.0 g. of VIII (1),⁴ 1.0 g. of potassium hydroxide, and 10 cc. of triethylene glycol, refluxed for ten hours, gave 1.3 g. of VI picrate, m.p. 134–136.5°.

Methiodide of VI (VII). The VI from 3.0 g. of picrate, 0.8 cc. of methyl iodide, and 5 cc. of methanol, allowed to stand for one hour, warmed to boiling, and diluted with ether, gave 2.3 g. (92%) of VII, m.p. 200–202°; prisms.

Anal. Calc'd for $C_{19}H_{23}IN$: C, 57.7; H, 6.7.

Found: C, 58.0; H, 6.6.

VII was also prepared in 90% yield on refluxing for six hours, 1.0 g. of V methiodide and 20 cc. of 25% sodium hydroxide.

Degradation of VII. (a) *Dibromo-1,1-diphenylbutane.*⁸ A mixture of 5.0 g. of VII, 40 cc. of water, and freshly prepared silver oxide (from 10 g. of silver nitrate) was heated on the steam-bath for fifteen minutes, shaken for two hours, warmed again, filtered, and the filtrate evaporated to dryness *in vacuo*. Distillation of the residue at 100–105° (0.1 mm.) gave 2.2 g. (90%) of liquid X.⁸ To 0.2 g. of this in 2 cc. of acetic acid was added dropwise 0.04 cc. of bromine and the solution diluted with a little water. Gradual cooling gave 0.2 g. (60%) of adduct, m.p. 55.5–57°; prisms from methanol, m.p. 55.5–56.5°.

Anal. Calc'd for $C_{18}H_{18}Br_2$: C, 52.2; H, 4.4.

Found: C, 52.5; H, 4.4.

(b) *1,1-Diphenylbutane (IX).* A mixture of 3.0 g. of X [see under (a)], 0.01 g. of platinum oxide, and 20 cc. of methanol absorbed one mole of hydrogen in one hour to give, on distillation of the product at 95° (0.05 mm.), 2.9 g. of IX, b.p. 102° (0.05 mm.), n_D^{21} 1.5601; lit. (6), b.p. 103–104° (0.05 mm.), n_D^{20} 1.5577.

Anal. Calc'd for $C_{16}H_{18}$: C, 91.4; H, 8.6.

Found: C, 91.5; H, 8.4.

⁸ No proof is offered for the location of the double bond in X.

Synthesis of 1,1-diphenylbutane. 1,1-Diphenyl-1-butanol was obtained in a yield of 60% from ethyl butyrate and phenylmagnesium bromide by the procedure of Schmidt and Hartmann (6). This carbinol (4.0 g.), 0.6 g. of 5% palladium charcoal, 35 cc. of acetic acid, and one drop of 60% perchloric acid absorbed 1.1 moles of hydrogen during five hours. The yield of evaporatively distilled IX was 3.4 g. (90%), b.p. 109.5–111° (0.5 mm.), n_D^{20} 1.5888. With palladium-barium sulfate the reduction time was twenty-four hours.

α,α -Diphenylvaleric acid. A mixture of 4.5 g. of α,α -diphenylvaleronitrile (1), 4.0 g. of potassium hydroxide and 23 cc. of triethylene glycol was refluxed for six hours. Ether and water were added, the aqueous phase was acidified, and the precipitate recrystallized from ethanol; yield of prisms 0.8 g., m.p. 150–152°. The acid was sublimed (130°/0.05 mm.) for analysis.

Anal. Calc'd for $C_{17}H_{19}O_2$: C, 80.3; H, 7.1.

Found: C, 80.5; H, 7.1.

From the ether phase, 0.7 g. of IX was obtained.

Nitration of 1,1-diphenylbutane. To 0.5 g. of IX (prepared by any of the three procedures above) cooled in water at 15° was added with shaking during three to five minutes, 1.5 cc. of nitric acid (d , 1.5). The mixture was warmed to homogeneity, diluted with water, cooled in ice, and the yellow viscous oil crystallized from 10 cc. of methanol to give 0.4 g. of dinitro-1,1-diphenylbutane, m.p. 113–118°. The analytical sample melted at 122–123°; prisms.

Anal. Calc'd for $C_{18}H_{18}N_2O_4$: N, 9.33. Found: N, 9.31.

SUMMARY

The hydrogenation of amidone to the carbinol, 6-dimethylamino-4, 4-diphenyl-3-heptanol, is described. O-Acyl derivatives of this carbinol are prepared in good yield, while reaction of the carbinol with chlorinating agents leads to a mixture of 3-chloro-6-dimethylamino-4,4-diphenylheptane and 6-dimethylamino-4,4-diphenylheptene-2.

In the reaction of amidone with alkali at 225°, scission of the ethyl keto group occurs.

BETHESDA 14, MARYLAND

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THE SYNTHESIS OF DL-LYSINE WITH C^{14} IN THE EPSILON POSITION¹PAUL OLYNYK, DAVID B. CAMP, ARVON M. GRIFFITH, SIEGFRIED
WOISLOWSKI, R. W. HELMKAMP*Received December 31, 1947*

In the attempt to prepare DL-lysine labeled with C^{14} for use in metabolic studies, our initial efforts were directed toward the development of a method which would permit the radioactive carbon to be introduced at a late stage in the process so that a large percentage of the C^{14} used would appear in the final product. The value of such a procedure would be increased if an intermediate formed prior to the introduction of the C^{14} offered the possibility of resolution into optically active forms. In accordance with these requirements, we sought to synthesize an α -acetamido- δ -halovaleric acid. It was hoped that this compound could be transformed by the action of $KC^{14}N$ into α -acetamido- δ -cyanovaleric acid, which on reduction of the cyano group and subsequent hydrolysis of the acetamido group should yield DL-lysine with C^{14} in the epsilon position.

Our attempts to prepare the desired valeric acid were unsuccessful. When equimolecular amounts of diethyl acetamidomalonate (*cf.* 1) and sodium ethoxide were refluxed in anhydrous ethanol with (a) an equimolar amount of 1-bromo-3-chloropropane (in the absence and in the presence of sodium iodide), (b) an equimolar amount of 1-chloro-3-iodopropane, and (c) four molar equivalents of 1,3-dibromopropane, oils were obtained from which no crystalline product other than unchanged acetamidomalonic ester could be isolated. Refluxing sodium acetamidomalonate (*cf.* 2) for approximately twenty-four hours with three molar equivalents of 1,3-dibromopropane in dioxane solution resulted in a practically quantitative formation of sodium bromide. However, nearly all of the acetamidomalonate was recovered from the reaction mixture (*cf.* 3).

Treatment of acetamidomalonate with 1-bromo-3-phenoxypropane in sodium ethoxide solution gave the expected product, diethyl acetamido-(3-phenoxypropyl)malonate. This ester was transformed by alkaline hydrolysis into α -acetamido- δ -phenoxyvaleric acid, and by heating with 48% hydrobromic acid into α -amino- δ -phenoxyvaleric acid (*cf.* 4), but attempts to cleave the ether linkage by refluxing the ester in an acetic acid solution of hydrogen bromide and in constant boiling hydriodic acid gave no satisfactory result.

Meanwhile the great reduction in the price of C^{14} made it less important that the introduction of the radioactive carbon occur in a late step in the synthesis. The feasibility of adapting a known procedure for preparing lysine to the production of this compound labeled with C^{14} was therefore considered. Of the methods described in the literature (5, 6, 7, 8, 9, 10), only that of von Braun (7) as improved by Eck and Marvel (9) and more recently by Galat (10) has been found

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to give a satisfactory yield. However, this synthesis offers no opportunity for introducing C^{14} , since the starting material (cyclohexanone or ϵ -caprolactam) already contains the six-carbon chain which appears in the lysine prepared from it. Of the remaining methods, that of Fischer and Weigert (5) seemed to be the most promising, even though their over-all yield was not high and the isolation of the lysine dihydrochloride by way of the phosphotungstate and picrate is cumbersome. We have succeeded in modifying their procedure so that their reaction sequence forms now the basis of a satisfactory method for preparing this amino acid.²

Below are summarized the steps in the synthesis and the principal modifications made in the original procedure which resulted in the yields indicated.

A. $KCN + Cl(CH_2)_3Br \xrightarrow{75-82\%} Cl(CH_2)_3CN$. The procedure was essentially that given in Organic Syntheses (11). However, since the object was to obtain maximum conversion of $KC^{14}N$ into $Cl(CH_2)_3C^{14}N$, two molar equivalents of 1-bromo-3-chloropropane to one of potassium cyanide were used. In order to obtain a high yield of the nitrile, an exhaustive extraction of the aqueous alcohol solution with chloroform was necessary. In the distillation, a cut was taken over a rather wide temperature range in order that it include the γ -bromobutyronitrile formed in the reaction, since obviously this compound can be used jointly with its chloro analog in step B.

B. $Cl(CH_2)_3CN + CH_2(COOC_2H_5)_2 \xrightarrow{74\%} NC(CH_2)_3CH(COOC_2H_5)_2$. The γ -chlorobutyronitrile was allowed to react with sodio-malonic ester (prepared by the action of alcohol-free sodium ethoxide on the ester) in an excess of the ester as solvent,³ first at room temperature and finally at that of the steam-bath.⁴

C. $NC(CH_2)_3CH(COOC_2H_5)_2 + C_2H_5ONO + NaOC_2H_5 \xrightarrow{70-83\%} NC(CH_2)_3C(=NOH)COOC_2H_5$. The alcohol was not removed, as in the procedure of Fischer and Weigert, by evaporation in a vacuum desiccator (*cf.* 12). Instead, the reaction mixture was diluted with ice-water and maintained at as near 0° as possible by further addition of ice during the subsequent extraction with ether, acidification, and reextraction with ether. It was found that washing the ether solution of the oximino ester with a solution of sodium bicarbonate removed most of the colored impurities, so that an almost white, crystalline product was obtained on evaporation of the ether.

D. $NC(CH_2)_3C(=NOH)COOC_2H_5 \xrightarrow{73\%} NH_2(CH_2)_4CHNH_2COOH \cdot HCl$ (recrystallized). The oximino ester was reduced catalytically (PtO_2) in acetic

² In a private communication, Professor A. J. Haagen-Smit has recently informed us that the synthesis of DL-lysine labeled with C^{14} in the epsilon position has also been accomplished by the Fischer and Weigert method at the California Institute of Technology.

³ The use of malonic ester as the solvent in this reaction was suggested to us by Dr. N. F. Albertson of the Winthrop Chemical Company.

⁴ The attempt was made to prepare γ -cyanopropylmalonic ester by inverting steps (A) and (B): $Cl(CH_2)_3Br \rightarrow Cl(CH_2)_3CH(COOC_2H_5)_2 \rightarrow NC(CH_2)_3CH(COOC_2H_5)_2$. While γ -chloropropylmalonic ester was obtained in good yield by the method of Fischer and Bergmann [*Ann.*, **398**, 120 (1913)], the nitrilation proceeded slowly and was accompanied by other reactions.

anhydride solution at 50–60° under a hydrogen pressure of 50–60 lbs./sq. in. The acetylated lysine ester was not isolated but was hydrolyzed directly to lysine dihydrochloride by refluxing it in hydrochloric acid solution. Conversion of the dihydrochloride into the monohydrochloride and recrystallization of the latter were carried out according to the directions in Organic Syntheses (13). The identity of the product was confirmed by its transformation into the dibenzoyl derivative.

To produce radioactive lysine monohydrochloride, HC^{14}N liberated on acidification of KC^{14}N [prepared by the method of Cramer and Kistiakowsky (14, 15, 16; cf. 17)] was absorbed in excess potassium hydroxide solution. After its cyanide content had been determined by titration with silver nitrate, the solution was acidified, the cyanide precipitated as silver cyanide, and the latter dissolved in a water-alcohol mixture containing a known amount of potassium cyanide. This solution was then used in the preparation of radioactive γ -chlorobutyronitrile. The over-all yield of the recrystallized lysine monohydrochloride, based on the cyanide used, was 28.4%; however, its activity per millimole was found to be only about 85% of the calculated.

EXPERIMENTAL

The preparation of KC^{14}N . The tubes used in the preparation of the radioactive potassium cyanide were heavy-walled Pyrex combustion tubes approximately 25 cm. long and 22 mm. o.d., drawn down to 4 mm. i.d. at each end. To connect the tube to the vacuum line in such a way that it could be rotated into either a horizontal or vertical position, a ground glass joint was sealed to one end at an angle of 120°. The other end was sealed into a test tube, 16 mm. o.d. to form a T. Into the latter was introduced potassium which had been weighed under toluene. After the toluene had been pumped off, the open end of the test tube was sealed, and the bomb tube, held horizontally, was evacuated with a mercury diffusion pump. The potassium, heated by a small direct flame, was gradually distilled into the bomb. From one to two grams of potassium could be deposited as a mirror on the wall of the bomb; if more was used in a run, it was collected in a small heap near the middle of the tube. The test tube was sealed off and discarded.

With the bomb tube in an almost vertical position, one millimole of carbon dioxide and two millimoles of ammonia per gram of potassium were frozen into it by use of liquid nitrogen. The quantities of gases were measured with a calibrated flask and a manometer attached to storage flasks. The carbon dioxide was generated by addition of concentrated sulfuric acid to the radioactive carbonate. The ammonia was cylinder ammonia passed over sodium hydroxide pellets.

The bomb tube was sealed off from the vacuum line, allowed to warm up for five minutes, then heated, with frequent rotation, for twenty minutes in a combustion furnace (30 cm. long), whose mid-point temperature was maintained at 630°. After the tube had been removed from the furnace and had cooled to room temperature, it was connected by wide-bored suction tubing to a dropping-funnel and a condenser attached to the vacuum line through a ground glass joint. The space to the bomb tube was evacuated, the tip of the bomb was broken off in the rubber tubing, and carbon dioxide-free water was allowed to drip into the tube from the dropping-funnel. After the excess potassium had reacted, the tube was removed from the vacuum line, and its contents were rinsed into a flask.

The determination of the cyanide in the solution could not be carried out directly by titration with silver nitrate because of the formation of a small amount of black precipitate (apparently free silver), which obscured the end-point. The solution was therefore acidified with dilute nitric acid, and the liberated hydrogen cyanide and carbon dioxide boiled

out and absorbed in 50% carbonate-free potassium hydroxide solution. To recover the carbonate, the alkaline solution was drained into saturated barium nitrate solution, and the precipitated barium carbonate filtered and washed in a carbon dioxide-free atmosphere. The cyanide in the filtrate was determined by titration with silver nitrate in the presence of ammonia and 0.1 millimole of potassium iodide as indicator. The solution was then acidified with nitric acid, and the cyanide precipitated by further addition of silver nitrate.

The barium carbonate used had an activity of 211 μ c. per millimole. The yields of cyanide in three runs with 1.06, 5.89, and 5.40 millimoles of carbonate were 70, 61 and 75% respectively. The average yield accordingly was 68%, and the total yield 8.40 millimoles. Approximately 18% of the radioactivity was recovered as barium carbonate.

Preparation of $\text{Cl}(\text{CH}_2)_3\text{C}^{14}\text{N}$. The precipitated radioactive silver cyanide obtained from the three runs mentioned above was filtered on a sintered glass funnel and as much as possible transferred with a spatula to a three-necked flask containing 18 g. of 95% potassium cyanide. The funnel and the spatula were then rinsed, first with a solution of 2 g. of 95% potassium cyanide in 20 ml. of water, and then with 10 ml. of water. Addition of these washings to the reaction flask produced a solution of 0.3 mole of cyanide in 30 ml. of water. After the solution had stood overnight, 100 g. of 1-bromo-3-chloropropane (0.6 mole) and 110 ml. of ethanol were added, and the mixture was refluxed for three hours. It was then treated with 120 ml. of water and 35 ml. of chloroform, and the aqueous layer was extracted six times with 40-ml. portions of chloroform. The combined chloroform extracts were repeatedly washed with 50-ml. portions of 20% calcium chloride solution and dried over calcium chloride. After decantation from the calcium chloride (which was then washed with additional chloroform), the solution was fractionally distilled, first at atmospheric pressure until a temperature of 120° was attained, and then under a pressure of 26 mm. The fractions boiling at 60–82° and 82–105° at the latter pressure were redistilled, and the product with the boiling range 90–100° collected; yield 23.4 g. (75%). In a preliminary run in which the cyanide used was non-radioactive, a yield of 82% was obtained.

Preparation of $\text{NC}^{14}(\text{CH}_2)_3(\text{COOC}_2\text{H}_5)_2$. A solution of 5.2 g. of sodium in 75 ml. of dry ethanol (18) was heated under diminished pressure on a steam-bath until no more solvent could be removed. Atmospheric pressure was then restored by permitting illuminating gas to enter the system. The white sodium ethoxide so obtained was cooled in ice-water, 127.6 g. of diethyl malonate (0.79 mole) was added, and the mixture was then shaken until complete solution of the ethoxide had occurred. By means of 75 ml. of dry ether, the 23.4 g. of radioactive γ -chlorobutyronitrile (0.226 mole) was rinsed into the reaction flask, and the mixture was allowed to stand overnight at room temperature. It was then refluxed on a steam-bath until evening, when the ether was removed as far as possible by distillation on a steam-bath. To ensure completeness of the reaction, the mixture was gently warmed under a reflux condenser on a steam-bath until the following morning. The precipitated sodium halides were taken up in ice-water, and the mixture was thoroughly extracted with ether. The ethereal solution was dried over sodium sulfate, concentrated on a steam-bath, and the residual oil was then subjected to fractional distillation under reduced pressure. After removal of the excess malonic ester, the distillation temperature rose rapidly to the boiling point of the product, which distilled at 138–143° at 1.1 mm., leaving only a small amount of colored material in the distilling flask; yield 38 g. (74%).

Preparation of $\text{NC}^{14}(\text{CH}_2)_3\text{C}(=\text{NOH})\text{COOC}_2\text{H}_5$. A solution of 37.9 g. of radioactive γ -cyanopropylmalonic ester (0.167 mole), 90 ml. of dry ethanol, and approximately 15 g. of ethyl nitrite (0.2 mole) was cooled in an ice-salt mixture contained in a large Dewar flask. An ice-cold solution of sodium ethoxide, prepared by dissolving 3.83 g. of sodium in 75 ml. of dry ethanol, was added, the Dewar flask was covered, and the mixture was allowed to stand for twelve hours. After addition of 500 ml. of ice-water, the solution was extracted three times with ice-cold ether (total volume 300 ml.), and the ether extracts in sequence washed with ice-water, which was then added to the original solution. While kept cold by immersion in an ice-bath, the aqueous solution was made acid to Congo Red by addition of 3 *N* hydrochloric acid. It was then extracted six times with ether (total volume 900 ml.).

The ether extracts were washed twice with a saturated solution of sodium bicarbonate and twice with water, and then combined. After the ethereal solution had been dried over sodium sulfate, it was concentrated by distillation on a steam-bath. The residue in the distilling flask was then rinsed with a small amount of ether into a crystallizing dish, warmed for a short time on a steam-bath, transferred to a vacuum desiccator, and the remaining solvent pumped off as the oximino ester crystallized. The product was then remelted on a steam-bath and again allowed to crystallize in the evacuated desiccator; yield 21.5 g. (70%); activity 4.6 μ c. per millimole. Yields of 83, 82, and 77% were obtained in three preceding runs in which the γ -cyanopropylmalonic ester was nonradioactive. In each of these runs the total volume of ethanol used (about 100 ml.) was less than in the run involving the radioactive ester, and the reaction mixture was kept not quite so cold and was allowed to stand for a somewhat longer period.

Preparation of $\text{NH}_2\text{C}^4\text{H}_2(\text{CH}_2)_3\text{CHNH}_2\text{COOH}\cdot\text{HCl}$. A mixture of 11.1 g. of the radioactive oximino ester, 60 ml. of acetic anhydride, and 0.3 g. of platinum oxide (Adams' catalyst) was shaken at 50° with hydrogen, the pressure of which was maintained at 50–60 lbs./sq. in. After about 65% of the amount of hydrogen corresponding to complete reduction of the cyano and oximino groups to amino groups had been absorbed, another portion of catalyst was added, and the temperature increased to 60°. When reduction was 85% complete, 20 ml. of acetic anhydride and a third portion of catalyst were added, the temperature was raised to 65°, and the shaking was continued until the calculated absorption of hydrogen had occurred.

After the acetic anhydride had been decomposed by treatment with cold water, the catalyst was filtered on a sintered glass funnel and washed with water. To hydrolyze the acetylated lysine ester, the filtrate was refluxed over night with one and one-half volumes of concentrated hydrochloric acid. The solution was then concentrated to a yellow syrup by heating under reduced pressure on a steam-bath. A small amount of concentrated hydrochloric acid was added to the residue, the solvent again evaporated, and this step repeated. The separation of the lysine dihydrochloride, its conversion into the monohydrochloride, and the recrystallization of the latter were carried out according to the procedures in Organic Syntheses (13); yield of recrystallized lysine monohydrochloride 8.0 g. (73%); m.p. 264–266° with decomposition; activity 5.0 μ c. per millimole.

It is important in the reduction of the oximino ester that the theoretical amount of hydrogen be absorbed. It was found that at 50° approximately 70% of the calculated decrease in pressure occurred usually within fifteen hours. However, for complete reduction three to five days were required, during which the temperature was increased to 65° and additional portions of catalyst were added. When the hydrogenation was discontinued after absorption had reached 80–85% of the theoretical, poor yields of lysine monohydrochloride were obtained.

Diethyl acetamido-(3-phenoxypropyl)malonate. This compound was prepared by refluxing a solution of 1 part of sodium, 9.35 parts of acetamidomalonic ester, and 10 parts of 1-bromo-3-phenoxypropane in 60 parts of absolute ethanol; yield of recrystallized product (from alcohol-water solution) 60.6%; m.p. 78.5°.

Anal. Calc'd for $\text{C}_{18}\text{H}_{25}\text{NO}_6$: C, 61.3; H, 7.2.

Found: C, 61.8; H, 7.0.

α -Acetamido- δ -phenoxyvaleric acid. A mixture of 3.2 g. of diethyl acetamido-(3-phenoxypropyl)malonate and 10 ml. of 20% sodium hydroxide solution was refluxed for two and one-half hours. It was then treated with 3.3 ml. of concentrated hydrochloric acid, refluxed for another hour, and filtered while hot. The product which separated on cooling was recrystallized from water; fine needles, melting at 150°.

Anal. Calc'd for $\text{C}_{13}\text{H}_{17}\text{NO}_4$: C, 62.1; H, 6.8.

Found: C, 62.3; H, 6.8.

α -Amino- δ -phenoxyvaleric acid. This compound was formed when diethyl acetamido-(3-phenoxypropyl)malonate was refluxed in 48% hydrobromic acid (1 g. of ester to 4.5 ml. of acid). Although it is not very soluble in water, it can be recrystallized from this solvent.

It dissolves readily in both alkali and acid, and when treated with ninhydrin solution, gives the color reaction obtained with α -amino acids. It melts with decomposition *ca.* 255°.

Anal. Calc'd for $C_{11}H_{16}NO_2$: C, 63.1; H, 7.2; N, 7.1.

Found: C, 63.7; H, 7.1; N, 6.9.

The radioactivity determinations were made by the method developed by Dr. William Bale and associates in the Radiology Department. The authors wish to acknowledge their indebtedness to Dr. Raymond Masters and his co-workers for carrying out these determinations.

SUMMARY

Improvements in the Fischer and Weigert synthesis of DL-lysine are described. DL-Lysine with C^{14} in the epsilon position has been prepared by this modified procedure.

ROCHESTER, N. Y.

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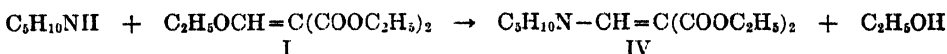
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THE 1-AMINO-2-NITROETHENES

CHARLES D. HURD AND L. T. SHERWOOD, JR.¹*Received January 19, 1948*

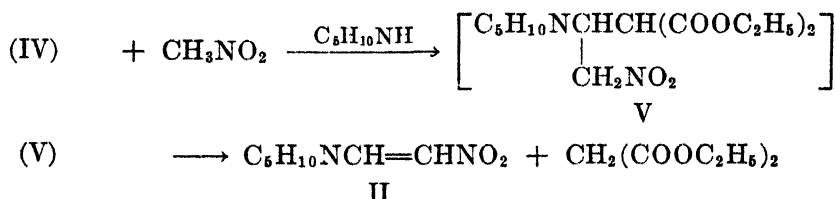
1-Amino-2-nitroethenes have not been previously reported. A few such compounds are described in this paper. These compounds are formed by interaction of ethyl ethoxymethylenemalonate (I) with nitromethane in the presence of certain amines. Two amines which are effective in this reaction are piperidine and morpholine, giving rise to 1-piperidino-2-nitroethene (II) and 1-morpholino-2-nitroethene (III), respectively.

Apparently the first step in the reaction is the rapid replacement of the ethoxy group of ethyl ethoxymethylenemalonate (1) to form, for example, ethyl piperidinomethylenemalonate (IV).



A similar reaction with arylamines gives rise to arylaminomethylenemalonate esters which have been used widely in recent years for the synthesis of quinoline derivatives (2).

The base-catalyzed addition of nitromethane to IV causes the formation of an unstable intermediate, ethyl (1-piperidino-2-nitroethyl)malonate (V), which decomposes immediately in the manner of a retrograde Michael reaction (3) to give II and ethyl malonate.

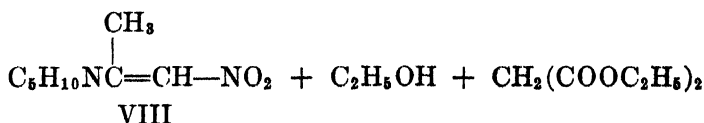
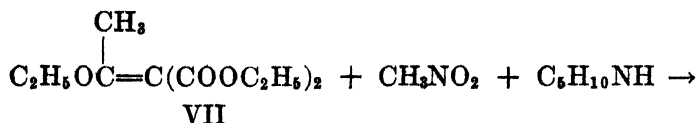


Strong evidence for the above formulation is the fact that if nitromethane is added in the presence of a catalytic amount of morpholine to ethyl morpholinomethylenemalonate (VI), the morpholino analog of IV, there results a good yield of III. Without catalyst, no reaction occurs.

It is not clear why piperidine and morpholine should be the only two amines out of several tested which yielded these aminonitroethenes. Dimethylamine, diethylamine, dipropylamine, pyrrolidine, and piperazine all failed to function when treated with nitromethane and ethyl ethoxymethylenemalonate.

Aminonitropropenes were prepared by methods resembling those used for the aminonitroethenes. Thus, by substitution of ethyl α -ethoxyethylidenemalonate (VII) (4) for I in the above reaction, one obtains 2-piperidino-1-nitro-1-propene (VIII) and 2-morpholino-1-nitro-1-propene (IX) as reaction products.

¹ Commercial Solvents Corporation Fellow, 1946-1947.



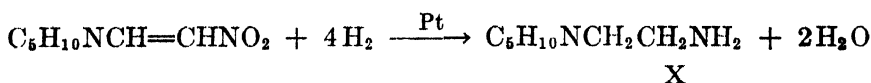
These two compounds were found to decompose on standing at room temperature for two months.

Evidence supporting the structure of II and its analogs were the reactions of hydrolysis, hydrogenation, and ozonolysis. Analysis and molecular weight determinations of II revealed the empirical formula $\text{C}_7\text{H}_{12}\text{N}_2\text{O}_2$, while the quantitative regeneration of piperidine by the action of aqueous alkali indicated a partial formula as follows: $\text{C}_5\text{H}_{10}\text{N}-\text{C}_2\text{H}_2\text{NO}_2$. This conclusion was proved by

TABLE I
THE AMINONITROETHENES AND AMINONITROPROPENES

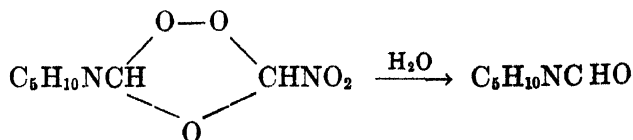
COMPOUND	FORMULA	M.P. °C	YIELD, %	N	
				Calc'd	Found
1-Piperidino-2-nitroethene	$\text{C}_7\text{H}_{12}\text{N}_2\text{O}_2$	95	40	17.94	17.57
1-Morpholino-2-nitroethene	$\text{C}_6\text{H}_{10}\text{N}_2\text{O}_3$	140-141	34.5	17.71	17.20
2-Piperidino-1-nitro-1-propene	$\text{C}_8\text{H}_{14}\text{N}_2\text{O}_2$	84	21.5	16.48	16.13
2-Morpholino-1-nitro-1-propene	$\text{C}_7\text{H}_{12}\text{N}_2\text{O}_3$	126-127	40	16.27	15.72

hydrogenation. Four moles of hydrogen were absorbed by II over a platinum oxide catalyst to give the expected N-(2-aminoethyl)piperidine (X):

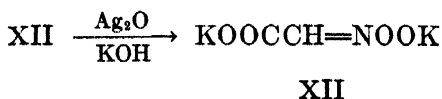
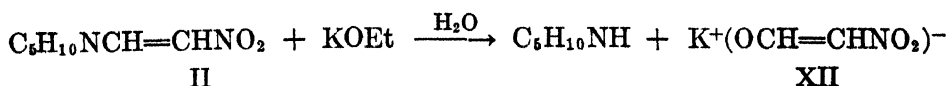


The diamine (X) was isolated as N-(2-benzamidoethyl)piperidine, which proved identical with the benzoyl derivative of the authentic diamine as independently prepared by the method of Gabriel (5). This proved that the nitrogens of II were separated by two carbon atoms and provided strong support for the proposed formula.

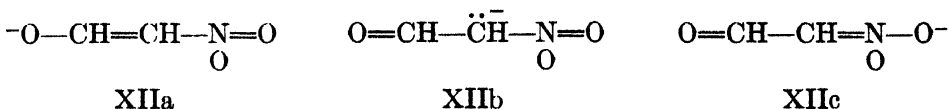
Finally, ozonolysis of II pointed to the presence of a carbon-to-carbon double bond. The isolation of formopiperidide as a reaction product established both the position of the double bond and the fact that a hydrogen was attached to the carbon adjacent to the piperidine nitrogen.



A study of other reactions of II disclosed its cleavage by potassium ethoxide into piperidine and a substance believed to be potassium *aci*-nitroacetaldehyde (XII). This contention was supported by conductivity data and by the fact that XII could be oxidized to potassium nitroacetate (XIII). These steps are summarized by these equations:



Nitroacetaldehyde (6) is itself unstable, and the enhanced stability of the potassium salt of nitroacetaldehyde may be attributed to resonance of the anion. Three important structures contributing to the resonance hybrid are XIIa, XIIb, and XIIc.



For conductivity measurements on this salt, standard conductivity equipment (7) was used. The resistance of an 0.0156 *M* aqueous solution of XII was 1270 ohms at 25.75° as measured with a Jones conductance bridge, a vacuum tube oscillator, an oscillograph and a cell of constant 2.23. The equivalent conductance, Λ , was then calculated.

$$\Lambda = \frac{1000 \times 2.23}{0.0156 \times 1270} = 111.5$$

This value of 111.5 is consistent with the formula assigned. A slow decrease in the resistance to 1214 ohms during a two-day period indicated decomposition.

Oxidation of II with silver oxide proceeded smoothly in the presence of a little potassium hydroxide to give a silver mirror, but to isolate the product, it was more convenient to oxidize XII. The potassium nitroacetate thus obtained was compared crystallographically with an authentic sample (6a) prepared by the action of concentrated potassium hydroxide on nitromethane. As nearly as could be readily determined, the two samples were identical.

This comparison was substantiated by the fact that both gave similar brown color reactions when treated with a ferric chloride solution. Both also gave a red colored reaction product with nitrous acid, in conformity with Victor Meyer's nitrolic acid test for the $-\text{CH}_2\text{NO}_2$ group (8).

Halogens and the hydrogen halides reacted instantly with II to give unstable solids which quickly turned into gummy substances. Bromine, for example, deposited a bulky precipitate when added to a cold solution of 1-piperidino-2-nitroethene in benzene. When this solid was collected on a filter and placed in a desiccator, it changed rapidly to a dark brown tar. Likewise, hydrogen bromide

caused precipitation (CCl_4 solution of II) but this product also was very unstable, tending to become tarry on standing either in the air or in a desiccator. When a solution of dry hydrogen chloride in ethyl ether was added to solid II the crystalline nature of the latter changed to a fluffy crystalline mass which was stable for a few hours. Analysis for chlorine (8.47%) suggested that one mole of hydrogen chloride and three moles of ether were added to one of the piperidino-nitroethene [calc'd for $\text{C}_7\text{H}_{13}\text{ClN}_2\text{O}_3 \cdot 3(\text{C}_2\text{H}_5)_2\text{O}$: Cl, 8.55].

Several new aminomethylenemalononic esters were prepared in the course of this investigation, namely, the derivatives related to piperidine, morpholine, diethylamine, and piperazine.

EXPERIMENTAL

The 1-amino-2-nitroethenes. Starting materials: Ethyl ethoxymethylenemalonate (I) was obtained from National Aniline Division of Allied Chemical and Dye Corporation and was redistilled at $130\text{--}133^\circ$ at 3 mm. Ethyl α -ethoxyethylidenemalonate was prepared essentially by the procedure of McElvain and Burkett (4).

The four compounds were prepared by the same general procedure, which is illustrated for 1-piperidino-2-nitroethene (II).

A mixture of 28 g. of ethyl ethoxymethylenemalonate, 17 g. of piperidine, and 17 g. of nitromethane was refluxed gently for two hours with an electric heater and transferred to a Claisen flask. Everything volatile at 100° and 12 mm. was removed by distillation and an equal volume of ether was added to the residue. After thorough mixing, the solution was chilled in a bath of dry-ice and acetone. Scratching the flask induced crystallization, and after about ten minutes, the crude product was removed and washed with cold ether until most of the tar had been removed and then was dissolved in about 100 g. of hot carbon tetrachloride. The solution was filtered and on cooling, 8.0 g. (40% yield) of II crystallized in the form of pale yellow, micaceous plates. Pertinent data are summarized in Table I. Other analytical data for 1-piperidino-2-nitroethene are as follows:

Anal. Calc'd for $\text{C}_7\text{H}_{12}\text{N}_2\text{O}_3$: C, 53.83; H, 7.74, mol. wt., 156.

Found: C, 53.80; H, 7.48; mol. wt., 157, 160.

Carbon tetrachloride was used to crystallize the piperidino compounds, while acetone-ether mixtures were best for the more insoluble morpholino analogs.

Alternate procedure: The preparation of 1-morpholino-2-nitroethene (III) from ethyl morpholinomethylenemalonate (VI). Ethyl morpholinomethylenemalonate was prepared by heating equimolar quantities of morpholine and I on a steam-bath for one hour. Dilution with ethanol and crystallization at -70° gave nearly quantitative yields of VI. An analytical sample melted at $64\text{--}66^\circ$.

Anal. Calc'd for $\text{C}_{12}\text{H}_{18}\text{NO}_5$: C, 56.02; H, 7.44.

Found: C, 56.34; H, 7.68.

A mixture of 5.94 g. of VI, 1.5 g. of nitromethane, and 0.3 g. of morpholine was heated for two hours in an oil-bath maintained at $140\text{--}150^\circ$. The volatile portion was distilled off as above and the product precipitated by the addition of ether followed by chilling to -70° . The yield was 1.61 g. (44%), m.p. $139\text{--}140^\circ$.

Ethyl piperidinomethylenemalonate and ethyl diethylaminomethylenemalonate. These two analogs of VI were prepared by the above procedure including the crystallization from ethanol at -70° . Both compounds melted at about room temperature.

Anal. (Piperidine derivative) Calc'd for $\text{C}_{12}\text{H}_{21}\text{NO}_4$: N, 5.49. Found: N, 5.60.

Anal. (Diethylamine derivative) Calc'd for $\text{C}_{12}\text{H}_{21}\text{NO}_4$: N, 5.76. Found: N, 5.53.

Alkaline hydrolysis of 1-piperidino-2-nitroethene (II). To 15 ml. of 10% potassium hydroxide solution was added 0.528 g. of II. The flask was swirled for thirty seconds to dissolve the solid. The liberated piperidine was converted to benzenesulfonpiperidide in the usual manner. A yield of 0.742 g. (97%) melting at $89\text{--}90^\circ$ was obtained.

Ozonization of 1-piperidino-2-nitroethene (II). A mixture of oxygen and ozone was

passed through a solution of 5.00 g. of II in 300 g. of chloroform. When the reaction was complete, as determined by the fact that no more ozone was absorbed, 100 g. of water was added to the solution. Air was bubbled through the mixture and it was gently warmed on a steam-bath. After the chloroform had been removed, the heating was continued until the temperature was 100° and maintained there for two hours. After cooling, the solution was extracted with five 25-ml. portions of ether. The extract was dried with magnesium sulfate. The solvent was removed and distillation of the residue produced 0.98 g. of formopiperidide. The index of refraction (n_D^{20}) of this fraction without further purification was 1.487 as compared to 1.485 for a synthetic specimen made from ethyl formate and piperidine.

The hydrogenation of 1-piperidino-2-nitroethene (II). Quantitative hydrogenation. A solution of 0.192 g. of II in 10 ml. of absolute ethanol was reduced in a semi-micro hydrogenation apparatus in the presence of 20 mg. of platinum oxide. At 751 mm. and 24°, 126 cc. (5.11×10^{-3} mole) was absorbed as compared with 4.94×10^{-3} mole calculated for the interaction of four moles of hydrogen with one mole of II.

Preparative hydrogenation. A solution of 0.547 g. of II in 20 ml. of absolute ethanol was hydrogenated in a Burgess-Parr apparatus in the presence of 30 mg. of platinum oxide and under 30 lb. of hydrogen pressure. The solution was acidified with 1 ml. of concentrated hydrochloric acid and evaporated to dryness. It was then dried under diminished pressure over phosphoric anhydride to remove all ethanol. The product was made alkaline with 10% potassium hydroxide solution and benzoylated with benzoyl chloride. Crystallization from an alcohol-water mixture gave 0.433 g. (54%) of N-(2-benzoylaminoethyl)piperidine, which after two recrystallizations, melted at 66.5–67.5°. This material showed no melting point depression with the benzoyl derivative of the amine as prepared by the method of Gabriel (5).

Anal. Calc'd for $C_{14}H_{20}N_2O$: N, 12.06. Found: 11.70.

Cleavage with potassium ethoxide. *The preparation and properties of the potassium salt of nitroacetaldehyde.* To a solution containing 1.00 g. of 1-piperidino-2-nitroethene in 30 ml. of absolute ethyl alcohol was added a potassium ethoxide solution consisting of clean potassium in about 20 ml. of absolute alcohol. A precipitate formed quickly, and the mixture was allowed to stand at –10° for thirty minutes. The salt was removed, washed twice with absolute ethanol, thrice with absolute ether, and allowed to dry in the air. The yield was 0.81 g. (100%).

On acidification of the filtrate of the above preparation with hydrochloric acid and taking it to complete dryness, a mixture of salts was obtained. This was dissolved in water, made basic, and treated with benzenesulfonyl chloride to give 1.44 g. (100%) of benzenesulfonpiperidide, m.p. 89–91°.

The salt of nitroacetaldehyde as prepared above is an almost white, fluffy crystalline solid. It is exceedingly soluble in water but is insoluble in organic solvents. It explodes on heating in a flame and melts with decomposition at 150–160°. It gave a fleeting brown color with ferric chloride solution and decomposed to a dark brown, water-soluble tar after standing for about six weeks. The analytical sample was dried in a desiccator but was not recrystallized.

Anal. Calc'd for $C_7H_7KNO_3$: K, 30.70. Found: K, 31.59, 31.63.

Oxidation of the potassium salt of nitroacetaldehyde. A mixture of 1.7 g. of the potassium salt, the moist silver oxide obtained from 10 g. of silver nitrate, 1.5 g. of potassium hydroxide, and 30 ml. of water was shaken overnight in a rotary shaker. The silver and the excess oxide were removed and the filtrate was evaporated under vacuum. The first crystals, about 0.5 g., were not of the desired compound. Addition of 10 ml. of ethanol threw out 1.4 g. of salt, which on recrystallization from 50% aqueous potassium hydroxide, gave the potassium nitroacetate for the crystallographic study previously discussed.

ACKNOWLEDGMENTS

Professor A. L. Howland of the Department of Geology, Northwestern University, performed the crystallographic comparisons. Microanalyses for nitro-

gen, carbon, and hydrogen were performed by Margaret Ledyard and Patricia Craig. Dr. Ralph Pearson of this department assisted in the electrical conductivity measurements.

SUMMARY

1-Piperidino-2-nitroethene, 1-morpholino-2-nitroethene, 2-piperidino-1-nitro-1-propene, and 2-morpholino-1-nitro-1-propene were prepared by interaction of piperidine or morpholine with ethyl ethoxymethylenemalonate or ethyl ethoxyethylidenemalonate and nitromethane. The steps in these processes and the limitations of the reaction have been expounded. Various reactions of 1-piperidino-2-nitroethene have been presented including alkaline hydrolysis to piperidine and nitroacetaldehyde, hydrogenation to N-(2-aminoethyl)piperidine, ozonolysis to formopiperidide, and reaction with bromine, hydrogen bromide, or hydrogen chloride.

EVANSTON, ILLINOIS

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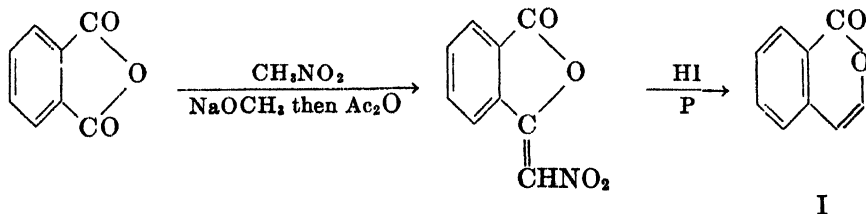
ISOCOUMARIN

H. W. JOHNSTON,¹ C. E. KASLOW, ARNE LANGSJOEN,² AND R. L. SHRINER²

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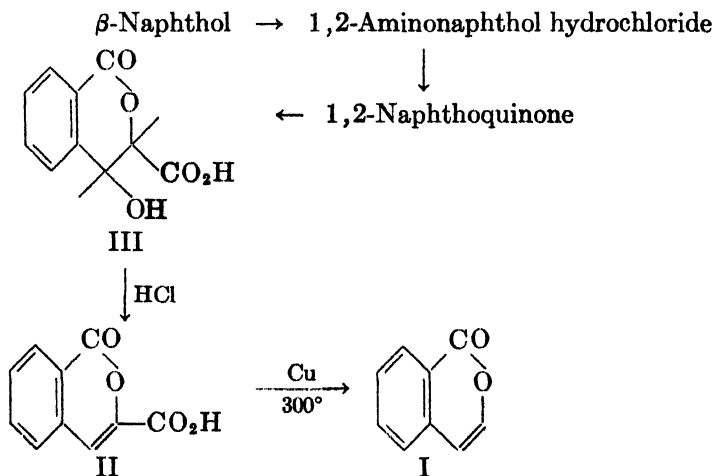
Isocoumarin (I) is an unusual unsaturated lactone, but its use has been limited by the fact that it is difficult to obtain in quantities suitable for research. The present report describes studies made on four methods of preparation.

One of the shortest syntheses is the following described by Gabriel (1).



The yield of nitromethylenephthalide is about 8% and the reduction gives only 22% yield so that the over-all yield is less than 2%. We have checked the yields reported by Gabriel but have been unable to improve them.

Bamberger and Frew (5) obtained low yields of isocoumarin (I) by heating the silver salt of 3-carboxyisocoumarin (II). The latter had been synthesized by Bamberger and Kitschelt (2) by the following sequence of reactions.



Since improved procedures have been described by Fieser (3) for the preparation of 1,2-naphthoquinone, the remaining steps in this synthesis were studied. It was found that calcium hypochlorite (4) was a better reagent for converting the 1,2-naphthoquinone to the δ -lactone of *o*-carboxyphenylglyceric acid (III) than sodium hypochlorite. If the temperature of the oxidation reaction was

¹ From a thesis submitted by H. W. Johnston to the Graduate School of Indiana University in partial fulfilment of requirements for the PH.D. in chemistry.

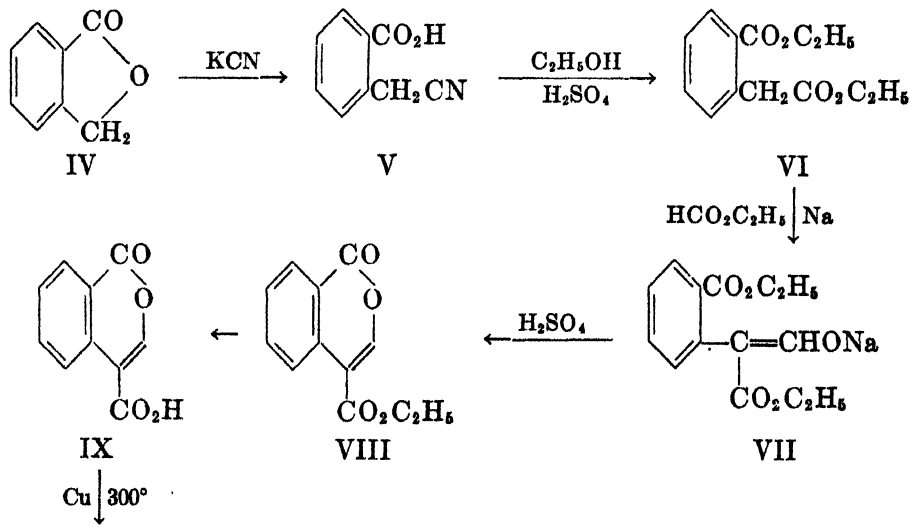
² Present address, State University of Iowa, Iowa City, Iowa.

kept at 5 to 10°, the lactone could be isolated as the calcium salt and so removed from the oxidizing medium by filtration. This salt was dissolved in hot hydrochloric acid solution and the desired lactone obtained in 46% yield. The conversion of the δ -lactone of *o*-carboxyphenylglyceric acid into 3-carboxyisocoumarin (II) was accomplished in 82% yields by heating the lactone with concentrated hydrochloric acid in a sealed tube at 160°.

Bamberger and Frew (5) prepared the silver salt of 3-carboxyisocoumarin (II), which was then mixed with a large amount of powdered clay and distilled. When this method was tried it was difficult to isolate the silver salt in even a reasonably pure state and the yield of isocoumarin was very poor (<1%). Hence a study of other procedures for decarboxylation of II was made, and it was found that heating the free acid with copper-bronze powder at 300°, followed by a flash distillation under reduced pressure gave a 65% yield of isocoumarin. The over-all yield from β -naphthol on the five steps was 11.6%.

A third synthesis, described by Dieckmann and Meiser (6), depended on the decarboxylation of 4-carboxyisocoumarin (IX). This acid was obtained by a condensation of ethyl homophthalate (VI) with ethyl formate, cyclization to ethyl isocoumarin-4-carboxylate (VIII), and hydrolysis to the acid (IX). The ethyl homophthalate was made by oxidation of naphthalene to phthalonic acid, reduction of this intermediate with hydriodic acid and red phosphorus to homophthalic acid, and esterification of the latter. The yields were low.

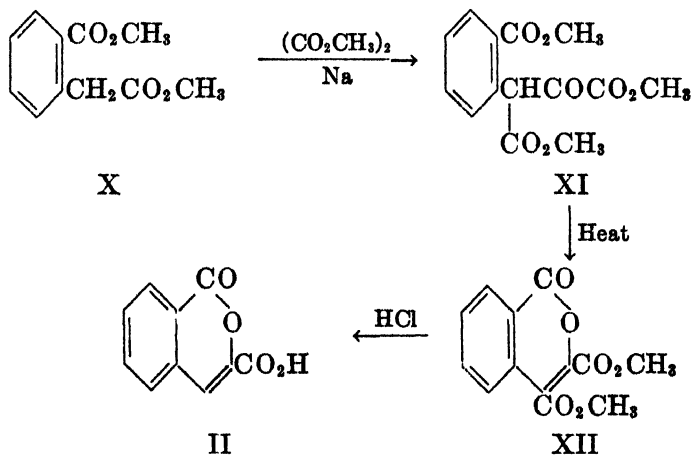
Two alternative methods are available for obtaining the intermediate ethyl homophthalate. Oxidation of indene by sulfuric acid and potassium dichromate gives a 58% yield of homophthalic acid (7), which can be esterified to VI. Also, *o*-carboxyphenylacetonitrile (V) is readily prepared (8) in 89% yields by the action of potassium cyanide on phthalide (IV). The nitrile (V) can be converted directly to ethyl homophthalate (VI). A combination of these reactions with those of Dieckmann above represented the best method for the preparation of 4-carboxyisocoumarin (IX).



In order to avoid losses, the intermediates, VII and VIII, were not isolated. Again, it was found that the 4-carboxyisocoumarin could be decarboxylated in 75% yields by heating it with metallic copper at 300°; a procedure and yield much better than heating the silver salt of IX or refluxing IX with sulfuric acid or phosphoric acid as mentioned by Dieckmann (6).

The over-all yield from phthalide by this series of reactions was 16.4%; a yield not much better than the second sequence. However, this third series does not require any sealed tube reactions, hence the quantities used can be increased so that satisfactory amounts of isocoumarin can be obtained.

Instead of using ethyl formate in the third step of the above synthesis, Vorozhtsov and Bogusevich (9) condensed methyl homophthalate (X) with methyl oxalate to produce the keto ester (XI). When heated at 100° the latter was cyclized to methyl isocoumarin-3,4-dicarboxylate (XII) which is hydrolyzed and decarboxylated by hot concentrated hydrochloric acid to isocoumarin-3-carboxylic acid (II).



Since Vorozhtsov and Bogusevich (9) reported a 48% yield of the isocoumarindicarboxylic ester, but gave no yield for the conversion to the 3-carboxyisocoumarin, this synthesis was also evaluated. Condensation of methyl homophthalate with methyl oxalate gave a 20% yield of the keto ester (XI), which when heated at 100° gave a 49% yield of XII. Refluxing XII with hydrochloric acid gave a 45% yield of isocoumarin-3-carboxylic acid (II) which was identical with the product obtained in the second series above. It was decarboxylated to isocoumarin in 65% yields. The over-all yield of isocoumarin calculated for the five steps from phthalide would be 7.0% and for the five steps from indene would be 7.3% using the highest yields reported for preparation of methyl isocoumarin-3,4-dicarboxylate. Lower yields were obtained when ethyl homophthalate and ethyl oxalate were used.

Through the courtesy of Dr. K. K. Chen of The Lilly Research Laboratories some pharmacological tests were made. The isocoumarin-3-carboxylic acid was about one-half as effective as dicoumarol in retarding clotting of the blood and isocoumarin caused only a transient fall in blood pressure in anesthetized cats.

EXPERIMENTAL

1,2-Aminonaphthol hydrochloride and 1,2-naphthoquinone. The procedures of Fieser (3) were used for the preparation of 1,2-aminonaphthol hydrochloride and its oxidation to 1,2-naphthoquinone. The over-all yield for these two steps was 51%.

*δ -Lactone of *o*-carboxyphenylglyceric acid.* The procedure given by Zincke (4) was modified as follows:—Five hundred grams of calcium hypochlorite (U.S.P.X. grade) was triturated with 500 ml. of distilled water and the undissolved solid material was collected on a Büchner funnel with suction. This residue was triturated in the same manner with 750 ml. of distilled water. After removal of the solid residue and repetition of the trituration with another 750-ml. portion of distilled water, the filtrates were combined and used. Forty-five grams (0.28 mole) of 1,2-naphthoquinone was mixed with enough water to form a thick paste, the mixture was chilled to 10° in an ice-salt bath, and 1 liter of the above calcium hypochlorite solution previously chilled to 0–5° was added in small portions with stirring.

A creamy white precipitate separated from the reaction mixture after a short time, which was collected on a filter with suction. The filtrate was discarded and the solid was dissolved in 250 ml. of hot water to which enough concentrated hydrochloric acid had been added to decompose the solid and effect complete solution (about 20 ml.). The clear amber solution was filtered to remove a small amount of gum and allowed to cool slowly. Yellow blades of the δ -lactone of *o*-carboxyphenylglyceric acid separated out. The product was dried at 100°, yield 27 g. (46%).

The product was sufficiently pure to be used in the next step. It may be purified by dissolving 53 g. of the yellow crystals in 500 ml. of hot water. Decolorizing carbon was added and the mixture was filtered with suction while hot. The treatment with decolorizing carbon was repeated and the clear filtrate was allowed to cool slowly. The product was obtained as white needles which were recrystallized three times from 250-ml. portions of hot water to yield colorless crystals of m.p. 207–209°. Bamberger (2) reported the melting point 204.5°. The recovery was 35 g.

3-Carboxyisocoumarin. Ten grams of the δ -lactone of *o*-carboxyphenylglyceric acid was placed in a 600 x 25 x 18 mm. Pyrex bomb-tube with 50 ml. of concentrated hydrochloric acid. The bomb was sealed and heated in a furnace at 160° for 16 hours. The large massive crystals were washed well with water. The yield was 7.5 g. (82%) of orange colored crystals, m.p. 242–244°. The product is pure enough for use in the preparation of isocoumarin, but it may be recrystallized from about 500 ml. of hot water. Two such recrystallizations yielded a crystalline product, m.p. 245–246°. Since Bamberger and Kitchelt (2) reported the melting point 237° and Vorozhtsov and Bogusevich (9) a value of 236°, the compound was analyzed.

Anal. Calc'd for $C_{10}H_6O_4$: C, 63.16; H, 3.18.

Found: C, 62.95; H, 3.16.

o-Carboxyphenylacetonitrile. The procedure of Price and Rogers (8) was followed with modifications. A mixture of 200 g. of phthalide and 200 g. of powdered potassium cyanide was placed in a 5-l. round-bottomed flask fitted with a stirrer having four wire paddles so placed that the sides of the flask were well scraped as the stirrer was rotated. From time to time stirring was stopped and a thermometer pushed down so that the tip was immersed in the reaction mixture and the temperature observed. The entire surface of the flask was heated in an electric heating mantle, and vigorous stirring was maintained. It was found that a good yield was obtained by controlling the rate of heating so that a maximum temperature of no more than 200° was reached over a period of one hour. The reaction temperature is critical. Stirring was continued at 200° for two to three hours. The solid mass was dissolved in 1 liter of water and a small amount of insoluble material removed by filtration. Concentrated hydrochloric acid was added with vigorous stirring until pH about 5 was obtained, and the solution became quite turbid. The acidity is determined with test paper and the solution should never become acid to Congo Red. If too much acid is added, the main product separates out as an oil in addition to the residue of homophthal-

imide which precipitates at this point. The mixture was filtered and decolorizing carbon (Norit) was added to the filtrate which was stirred for several minutes and again filtered.

The product was precipitated by the rapid addition of 50 ml. of concentrated hydrochloric acid. The mixture was chilled in an ice-bath and crystallized; yield 213 g. (89%) of white crystals which melted at 113–117°.

Ethyl homophthalate. In a 1-liter three-necked flask equipped with a mechanical stirrer, reflux condenser, and a dropping-funnel were placed 161 g. (1 mole) of *o*-carboxyphenylacetonitrile and 400 ml. of 95% ethanol. The mixture was cooled in an ice-bath and stirred while 196 g. (2 moles, 109 ml.) of concentrated sulfuric acid was added dropwise over a period of about one-half hour.

After complete addition of the acid, the stirrer and dropping-funnel were replaced by a reflux condenser and the mixture was refluxed for 12 hours. It was poured into 1 liter of water and a small amount of insoluble material was removed by filtration. The aqueous solution was extracted with 1 liter of ether and then with two 500-ml. portions of ether. The ether extracts were combined and washed four times with 200-ml. portions of water, three times with 100-ml. portions of 10% sodium carbonate, and, finally, twice with 200-ml. portions of distilled water. The ether solution of the product was dried over magnesium sulfate and the ether was distilled. The residue was distilled under reduced pressure. After separating a small amount of forerun up to 164°/19 mm. the main fraction of ethyl homophthalate was collected at 164–169° at 19 mm. The yield was 133 g. (56%) of a product having an index of refraction, n_D^{20} 1.5072.

4-Carboxyisocoumarin. In a 1-liter three-necked round-bottomed flask was placed 23 g. of powdered sodium which was covered with 100 ml. of absolute ether. A reflux condenser protected by a calcium chloride drying tube, a mechanical stirrer and a dropping-funnel were fitted to the flask which was immersed in an ice-salt bath.

A mixture of 236 g. (1 mole) of ethyl homophthalate and 81.4 g. (1.1 mole) of freshly distilled dry ethyl formate was dissolved in an equal volume of absolute ether and placed in the dropping-funnel. A small amount of ethyl formate was added to the reaction flask through the condenser to start the reaction and the mixed esters in the dropping-funnel were then added at a slow rate. The start of the reaction was indicated by the formation of gas bubbles and the development of a red color in the mixture. The reaction was vigorous but it was easily controlled in the cold. The reaction mixture was stirred three hours at room temperature after complete addition of the reagents. A small amount of ethyl formate was then added to use up a little unreacted sodium. The reaction mixture was allowed to stand overnight at room temperature, treated with 100 ml. of water and 200 ml. of ether, and extracted. The red aqueous layer was washed twice with 100-ml. portions of ether, which were discarded. Dilute sulfuric acid (6 *N*) was added with stirring to the aqueous mixture until it was acid to Congo Red. The product was a yellow oil which was removed and the acid aqueous layer was extracted twice with 100-ml. portions of ether which were added to the main product. The ether solution of the product was washed three times with 150-ml. portions of water to remove excess mineral acid, after which the ether was removed by distillation. To the residual oil were added 150 ml. of glacial acetic acid and 150 ml. of concentrated hydrochloric acid and the mixture was heated at reflux temperature for sixteen hours. A yellow granular solid separated out during the heating period. The flask was allowed to cool slowly to room temperature and the 4-carboxyisocoumarin was recrystallized twice from 2 l. of hot 95% ethanol. Short needles, slightly yellow in color, were obtained, m.p. 250–252°. The yield was 84 g. (44%). This product was sufficiently pure for the preparation of isocoumarin.

A 10-g. portion was purified further by dissolving it in 250 ml. of hot ethanol and adding Norit. The hot filtrate was allowed to cool slowly to room temperature, and gave 6 g. of white needles melting at 249–251°. A second crystallization raised the melting point to 251–252°. Since Dieckmann and Meiser (6) reported the melting point 244° the acid was analyzed.

Anal. Calc'd for $C_{10}H_8O_4$: C, 63.16; H, 3.18.

Found: C, 63.21; H, 3.03.

Methyl isocoumarin-3,4-dicarboxylate. The procedure described by Vorozhtsov and Bogusevich (9) was followed. A mixture of 20 g. of methyl homophthalate, 11.9 g. methyl oxalate, 2.3 g. powdered sodium in 100 ml. absolute ether was stirred at 25° for 46 hours. The mixture was decomposed by addition of 150 ml. of water and acidified with 5% sulfuric acid. Extraction with four 50-ml. portions of ether gave 5.9 g. (20.8%) of the keto ester. In order to avoid losses this was not purified but was heated at 100° for two hours to give 5.2 g. of crude ester. This was recrystallized from 75 ml. of hot methanol to give 2.6 g. (49%) of methyl isocoumarin-3,4-dicarboxylate which melted at 130.5–131.7°, (lit. value 134°).

3-Carboxyisocoumarin. Two grams of the above di-ester was refluxed for two hours with 100 ml. of concentrated hydrochloric acid. When cooled, 0.8 g. of crude 3-carboxyisocoumarin separated, which melted at 238–240°. It was purified by solution in dilute alkali, filtration, and acidification. This product was twice recrystallized from hot water, yielding 0.6 g. (45%) of white crystals which melted at 246–247° and did not depress the melting point of the 3-carboxyisocoumarin prepared from the δ -lactone of *o*-carboxyphenylglyceric acid. When mixed with 4-carboxyisocoumarin (m.p. 251–252°) a marked depression in melting point of the mixture to 211–216° occurred. This confirms the structure of the product obtained by hydrolysis and decarboxylation of methyl isocoumarin-3,4-dicarboxylate as the 3-carboxyisocoumarin.

Isocoumarin. (a) *From 3-carboxyisocoumarin.* A 125-ml. Claisen flask was arranged for distillation with a 125-ml. distilling flask, water cooled, as a receiver. Eight grams (0.042 mole) of 3-carboxyisocoumarin was mixed with 0.128 g. of copper-bronze powder and heated to 300° with a metal-bath. The side arm of the receiver was extended just under the surface of a beaker of water so that the progress of the decarboxylation could be followed by observation of the rate of formation of gas bubbles. The compound melted to a brown liquid which rapidly lost carbon dioxide on continued heating. As soon as a rapid evolution of bubbles ceased, the beaker of water was removed from the side arm of the receiver and an aspirator was attached which reduced the pressure to about 20 mm.

Isocoumarin was rapidly removed in this manner from the hot reaction flask and was collected as a yellow oil which crystallized rapidly when cooled. The solid product was dissolved in 10 ml. of methanol at about 50°. Distilled water was added dropwise to the methanol solution until a turbidity just appeared, a few drops of methanol were added to clarify the solution, and it was rapidly chilled in the refrigerator. Colorless platelets were obtained, m.p. 43–46°. The recrystallization procedure was repeated three times with methanol-water mixtures in the ratio of approximately 5 ml. methanol to 3 ml. water. The yield of isocoumarin of melting point, 44–45° was 4 g. (65%).

(b) *From 4-carboxyisocoumarin.* In a 125-ml. Claisen flask equipped with a thermometer and a 50-ml. distilling flask as a receiver was placed a mixture of 38 g. (0.2 mole) of 4-carboxyisocoumarin and 0.9 g. (0.014 mole) of copper-bronze powder. It was heated to about 270–300° in a metal-bath. A rapid evolution of carbon dioxide took place which was followed as above. After all of the carbon dioxide was driven off at atmospheric pressure, the apparatus was connected to an aspirator and the mixture was flash distilled.

The yellow liquid which collected in the receiving flask was transferred to a 50-ml. boiling-flask connected to a 3-inch Vigreux column. The product was then distilled at 20 mm. pressure and collected at 155–156°. The clear, almost odorless distillate was taken up in 1500 ml. of petroleum ether (b.p. 30–60°) and allowed to crystallize in an ice-box. White needles were obtained having the melting point 44–46°. The mother liquor was evaporated to one-half its original volume to recover another crop of crystals of melting point 43.5–45°. The total yield was 22 g. (75%). The product is sufficiently pure for synthetic purposes but may be recrystallized again from petroleum ether to give isocoumarin of melting point 45–46°. Gabriel (1) has reported the melting point 46° and Bamberger and Frew (5) the value 47°.

SUMMARY

Isocoumarin may be obtained in 65 and 75% yields by decarboxylation of 3- and 4-carboxyisocoumarin respectively using copper powder as a catalyst at 300°.

A comparison of the methods for the preparation of isocoumarin indicates that the most practical sequence involves the condensation of ethyl homophthalate with ethyl formate to ethyl isocoumarin-4-carboxylate, hydrolysis to the acid, and decarboxylation.

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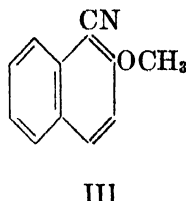
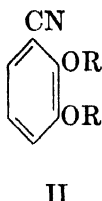
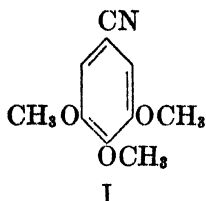
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THE ACTION OF GRIGNARD REAGENTS ON 2-METHOXY-1-NAPHTHONITRILE

REYNOLD C. FUSON AND DAVID H. CHADWICK¹*Received February 9, 1948*

The replacement of a nuclear alkoxy group by the action of a Grignard reagent appears to have been realized first by Haller and Schaffer (1), who prepared a compound believed to be 3,5-dimethoxy-4-butylphenyl isobutyl ketone by the interaction of isobutylmagnesium bromide and 3,4,5-trimethoxybenzonitrile (I). This result was confirmed later by Hurd and Winberg (2). Similar replacements were observed by Fuson and Speck, working with certain *o*-methoxyaryl mesityl ketones (3). Later Richtzenhain found that various Grignard reagents brought about replacement of 2-alkoxy groups in 2,3-dialkoxybenzonitriles (II) (4, 5).



Since in the hindered ketones the replacement of methoxyl groups occurred more readily in the naphthalene than in the benzene series, it seemed probable that the methoxy nitriles of the naphthalene series might suffer replacement of the alkoxy group more readily than those studied by Richtzenhain. With this idea in mind we prepared 2-methoxy-1-naphthonitrile (III) and treated it with ethylmagnesium bromide. A high yield was obtained of the product of 1,2 addition; there was no evidence that replacement of the methoxyl group had occurred. Benzylmagnesium chloride was found to react in a similar fashion.

The results obtained in an attempt to hydrolyze the imine resulting from addition of ethylmagnesium bromide to 2-methoxy-1-naphthonitrile are interesting. The product consisted of a small amount of the expected ketone, 1-propionyl-2-naphthol, accompanied by substantial amounts of β -naphthol and methyl β -naphthyl ether. The supposition that the latter products arise from hydrolytic cleavage of the ketone initially formed was substantiated by demonstrating that the ketone did, indeed, give rise to these products under the conditions of the original hydrolysis. A similar observation in regard to 10-methoxy-9-anthryl methyl ketimine was reported by Krollpfeiffer (6). 7-Methoxy-8-chloro-9-acetyltetrahydrophenanthrene was found by Kupchan and Elderfield (7) to behave in a similar way.

From a survey of the literature (8-15) it is evident that the ease of hydrolytic cleavage of alkyl aryl ketones in acidic media parallels the difference in electro-

¹ Present address: The Monsanto Chemical Company, Anniston, Alabama.

negativity of the alkyl and aryl groups. A similar parallel has been noted (16) with respect to the hydrolytic stability of carboxylic acids.

EXPERIMENTAL²

2-Methoxy-1-naphthonitrile. A. *From 1-bromo-2-methoxynaphthalene.* A solution of 40 g. of bromine in 100 ml. of glacial acetic acid was added, dropwise and with stirring, over a period of one hour to a solution of 39.5 g. of methyl β -naphthyl ether in 350 ml. of the same solvent. The product which separated was removed by filtration, and the remainder precipitated by pouring the filtrate into water. The crude 1-bromo-2-methoxynaphthalene weighed 53 g. (93% yield); m.p. 82–84°. This compound had been prepared previously by the action of phosphorus pentabromide on methyl β -naphthyl ether (17) and by the methylation of 1-bromo-2-naphthol (18). Its melting point was reported as 83–84° (17) and 85° (18).

The 1-bromo-2-methoxynaphthalene was converted to 2-methoxy-1-naphthonitrile by a procedure similar to that used by Newman (19) to prepare α -naphthonitrile from α -bromo-naphthalene. The 2-methoxy-1-naphthonitrile separated from methanol in the form of white needles; m.p. 95–96°; yield 90%.

B. *From methyl β -naphthyl ether and cyanogen bromide.* The procedure was that employed by Karrer, Rebmann, and Zeller (20). From 20 g. of cyanogen bromide and 39.5 g. of methyl β -naphthyl ether was obtained 6 g. (13% yield) of 2-methoxy-1-naphthonitrile, m.p. 94–96°.

C. *From 2-methoxy-1-naphthaldehyde.* The aldehyde was made in 60% yields by a procedure similar to that employed by Wood and Bost (21) to prepare 2-ethoxy-1-naphthaldehyde. The product was purified by recrystallization from methanol; m.p. 81–84° (22). The aldehyde was converted to the corresponding oxime by the method of Brady and Goldstein (23). The yield of product twice recrystallized from benzene was 84%; m.p. 149–153°. A solution of 10 g. of the oxime in 40 ml. of acetic anhydride was heated under reflux for one hour and poured into water, with vigorous stirring. The crude product (99% yield) melted at 93–95°.

1-Bromo-2-ethylnaphthalene. 2-Ethylnaphthalene was prepared in 58% yield by reducing methyl β -naphthyl ketone according to Martin's modification (24) of the Clemmensen method. A solution of 80 g. of bromine in 75 ml. of carbon tetrachloride was added, dropwise with stirring, over a period of two hours to a mixture of 78 g. of 2-ethylnaphthalene, 250 ml. of carbon tetrachloride, a pinch of iron powder, and a crystal of iodine. During the addition and for two hours afterward the reaction mixture was cooled in an ice-bath and protected from light. The 1-bromo-2-ethylnaphthalene, isolated by conventional procedures, boiled at 125–126° (3 mm.); yield 75%. Analysis indicated that it was not quite pure: presumably, the contaminant was 2-ethylnaphthalene.

Anal. Calc'd for $C_{12}H_{11}Br$: C, 61.29; H, 4.72.

Found: C, 62.42; H, 4.91.

2-Ethyl-1-naphthonitrile. The procedure was similar to that employed by Newman (19) for the preparation of α -naphthonitrile. A yield of 15 g. (81%) of 2-ethyl-1-naphthonitrile (m.p. 63–67°) was obtained from 23.5 g. of the corresponding bromide. The nitrile was recrystallized from high-boiling petroleum ether; m.p. 66.5–67.5°.

Anal. Calc'd for $C_{13}H_{11}N$: C, 86.15; H, 6.12.

Found: C, 86.94; H, 6.42.

2-Ethyl-1-naphthoic acid. A solution of a Grignard reagent, prepared from 23.5 g. of 1-bromo-2-ethylnaphthalene, 2.45 g. of magnesium, and 60 ml. of dry ether, was poured on a large excess of solid carbon dioxide. The acid was isolated in the usual way and purified by repeated recrystallization from benzene; m.p. 118–119°; the yield of crude product was 76%.

Anal. Calc'd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04.

Found: C, 77.82; H, 6.23.

² Microanalyses were by Misses Theta Spoor, Betty Snyder, and Jane Wood.

2-Ethyl-1-propionaphthone. 2-Ethyl-1-naphthoyl chloride was prepared in 85% yield by treatment of the acid with thionyl chloride; b.p. 129–131° (2–3 mm.). A solution of 12 g. of the acid chloride in 50 ml. of dry ether was added slowly to a Grignard reagent prepared from 16.4 g. of ethyl bromide, 3.65 g. of magnesium, and 70 ml. of ether. The reaction mixture was allowed to reflux during the addition and for thirty minutes afterward and was poured into a chilled solution of aqueous ammonium chloride. The ketone, isolated in the usual way, crystallized from ethanol in diamond-shaped plates; m.p. 77–78°; yield 86%.

Anal. Calc'd for $C_{15}H_{16}O$: C, 84.81; H, 7.60.

Found: C 84.76; H, 7.88.

Treatment of the ketone with hydroxylamine failed to convert it to an oxime.

1-Propionyl-2-naphthol. This compound was made by rearrangement of β -naphthyl propionate, the procedure of Gulati, Seth, and Venkataraman (25). The product separated from dilute acetic acid in leaflets and from high-boiling petroleum ether in cubes. The pure 1-propionyl-2-naphthol had a light yellow color; m.p. 82–84°.

Anal. Calc'd for $C_{15}H_{14}O_2$: C, 77.98; H, 6.04.

Found: C, 77.99; H, 6.13.

The melting point recorded by Gulati, Seth, and Venkataraman, however, was 70–71°. Because of the discrepancy in melting point values we converted our sample into 2-methyl- β -naphthoflavone according to the directions of Gulati, Seth, and Venkataraman. Our product melted at 109–109.5°, theirs at 110°.

Anal. Calc'd for $C_{20}H_{14}O_2$: C, 83.89; H, 4.92.

Found: C, 83.66; H, 5.06.

1-Propionyl-2-methoxynaphthalene. A mixture of 20 g. of 1-propionyl-2-naphthol, 100 ml. of 2 *N* sodium hydroxide solution, and 9.3 ml. of methyl sulfate was shaken mechanically for twenty hours at room temperature. An additional 15 ml. of sodium hydroxide solution (35%) was added, and the mixture heated under reflux for six hours. The ketone, isolated by usual methods, was a nearly colorless oil boiling at 141–143° at 2–3 mm.; n_D^{20} 1.6013.

Anal. Calc'd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59.

Found: C, 78.01; H, 6.68.

The compound was also made by condensing 2-methoxy-1-naphthoyl chloride with ethylmagnesium bromide. The acid chloride (m.p. 67–71°) was prepared by way of the acid from 1-bromo-2-methoxynaphthalene by the method of Bretscher, Rule, and Spence (26).

A third method of preparation involved the condensation of propionic anhydride with methyl β -naphthyl ether in the presence of aluminum chloride. The anhydride (39 g.) was added over a period of thirty minutes to a mixture of 40 g. of the ether, 100 ml. of carbon disulfide, and 74 g. of aluminum chloride. The product weighed 34.7 g.; b.p. 144–147° (3 mm.). In a similar experiment in which propionyl chloride was the acylating agent, 8.5 g. of 1-propionyl-2-methoxynaphthalene was obtained from 15.8 g. of methyl β -naphthyl ether. In the condensation with propionyl chloride a solid by-product, presumably a position isomer, was isolated. It was recrystallized from methanol; m.p. 110–111°.

Anal. Calc'd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59.

Found: C, 78.99; H, 6.66.

Reaction of ethylmagnesium bromide and 2-methoxy-1-naphthonitrile: Acid hydrolysis of 2-methoxy-1-propionaphthimine. A solution of 11 g. of 2-methoxy-1-naphthonitrile, 50 ml. of dry benzene, and 50 ml. of dry ether was added over a period of ninety minutes to a refluxing solution of a Grignard reagent prepared from 2.92 g. of magnesium, 14.0 g. of ethyl bromide, and 50 ml. of dry ether. The mixture was heated under reflux for an additional four hours and poured into a chilled ammonium chloride solution. The ether layer was washed three times with 10% sodium hydroxide solution, once with saturated sodium chloride solution, five times with 1/1 hydrochloric acid, and three times with saturated sodium chloride solution. In all cases the combined aqueous extracts were back-washed once with ether and the ether wash returned to the main ether layer.

The ether layer was evaporated, and the residual crystals purified by recrystallization from high-boiling petroleum ether; 1 g. of unchanged 2-methoxy-1-naphthonitrile was re-

covered. Evaporation of the petroleum ether filtrate left only a small amount of residue, indicating that very little, if any, 2-ethyl-1-naphthonitrile had been formed.

The hydrochloric acid extract was made alkaline with ammonia and extracted with ether. The ether extract was washed with aqueous sodium chloride solution and evaporated. The remaining oil was dissolved in 150 ml. of 1/1 hydrochloric acid and heated under reflux for three hours; an oil separated during this period, and was extracted with ether (A). Neutralization of the extracted acid solution precipitated an appreciable quantity of unhydrolyzed imine.

The ether solution (A) was extracted with dilute sodium hydroxide solution (B) and washed with aqueous sodium chloride solution. After the solvent had been removed by evaporation, the oily residue was dissolved in hot low-boiling petroleum ether. When the solution was cooled, 2 g. of solid separated which melted at 60–65°. Further recrystallization of the compound from high-boiling petroleum ether raised the melting point to 72–74°. The melting point was not depressed when the substance was mixed with methyl β -naphthyl ether.

Evaporation of the low-boiling petroleum ether filtrate left after removal of the methyl β -naphthyl ether, allowed the recovery of about 2 ml. of light-colored oil. This material was separated from remaining traces of methyl β -naphthyl ether by distillation under diminished pressure, and that portion of the distillate collected above 120° (3 mm.) was carefully redistilled from a very small modified Claisen flask. The main portion boiled at 152–154° (3–4 mm.); n_D^{20} 1.6010. The boiling point and refractive index identify this substance as 1-propionyl-2-methoxynaphthalene.

Acidification of the sodium hydroxide extract (B) precipitated a solid (1.7 g.) which melted at 116–120° without further purification and showed no depression of melting point when mixed with an authentic sample of β -naphthol. When treated with bromine in carbon tetrachloride this compound gave a derivative which was recrystallized twice from dilute ethanol. It formed long fine needles which melted at 81–83°. 1-Bromo-2-naphthol melts at 84° (27).

Hydrolysis of 1-propionyl-2-methoxynaphthalene. A suspension of 11 g. of the ketone in 150 ml. of 1/1 hydrochloric acid was heated under reflux for three hours, cooled, and extracted with ether. The ether extract, after being washed with dilute sodium hydroxide and saturated sodium chloride solution, was dried over calcium chloride and evaporated. The remaining oil, 9.3 g., was distilled under diminished pressure. Three fractions were collected. The lower-boiling fraction distilled at 95–100° (3–4 mm.) and amounted to 0.8 g. This material solidified in the receiver and melted at about 65° without further purification, and at 71–73° after recrystallization from high-boiling petroleum ether. The melting point was not depressed by mixing with an authentic sample of methyl β -naphthyl ether. About 0.2 g. was heated under reflux for fifteen minutes with 5 ml. of glacial acetic acid and 5 ml. of 48% hydrobromic acid and poured on ice. The precipitate was removed by filtration and dried. After recrystallization from high-boiling petroleum ether, the light orange colored plates melted at 119–122° and did not show a depression of melting point when mixed with an authentic sample of β -naphthol. The low-boiling fraction was therefore β -naphthyl methyl ether.

The second fraction (1.8 g.) distilled between 100° and 140° (3–4 mm.), the first few drops of distillate solidifying in the receiver. It was evidently a mixture and was not investigated further. The high-boiling fraction distilled at 152–154° (3–4 mm.) and weighed 6.0 g.; n_D^{20} 1.6041. On the basis of boiling point and refractive index it was assumed to be starting material.

The sodium hydroxide extract was washed once with ether and acidified with hydrochloric acid. The precipitate was dried (0.7 g.), and recrystallized from high-boiling petroleum ether; m.p. 116–119°. It did not depress the melting point of an authentic sample of β -naphthol. Its bromo derivative melted at 80–83°.

Reaction of benzylmagnesium chloride with 2-methoxy-1-naphthonitrile. A solution of the nitrile (11 g.) in 50 ml. of dry benzene and 50 ml. of dry ether was added over a period of

sixty minutes to a solution of benzylmagnesium chloride prepared from 2.92 g. of magnesium, 16 ml. of benzyl chloride, and 150 ml. of dry ether. An orange-red precipitate formed as the nitrile solution entered the Grignard solution; the color faded as mixing proceeded. After being stirred overnight at room temperature the reaction mixture was heated under reflux for four hours, cooled, and poured into cold dilute hydrochloric acid. Some of the imine hydrochloride separated as a white solid and remained with the aqueous layer when the ether layer was removed. From the ether layer by usual procedures were isolated 2.3 g. of unchanged 2-methoxy-1-naphthonitrile and about 1 g. of a solid (m.p. 52–54°) believed to be bibenzyl.

A portion of the crude imine hydrochloride was washed with ether, dried, and analyzed. The composition of the salt approximated that of the hydrochloride of the imine formed by 1,2 addition.

Anal. Calc'd for $C_{19}H_{18}ClNO$: C, 73.18; H, 5.82.

Found: C, 71.90; H, 6.19.

A second portion of the imine hydrochloride was dissolved in ammoniacal ether, reprecipitated with hydrogen chloride, triturated with concentrated hydrochloric acid, washed with ether, and dried. It melted at 192–193°.

SUMMARY

Ethylmagnesium bromide and benzylmagnesium chloride have been found to react normally with 2-methoxy-1-naphthonitrile; no replacement of the methoxyl group was observed.

1-Propionyl-2-methoxynaphthalene has been found to undergo hydrolytic cleavage with loss of the acyl group when heated with dilute hydrochloric acid.

URBANA, ILL.

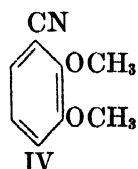
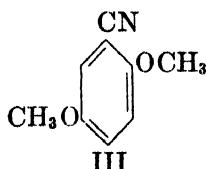
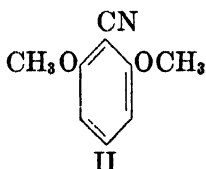
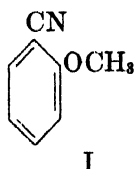
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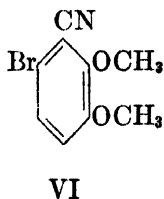
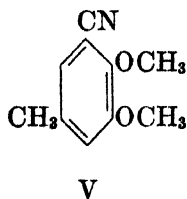
REPLACEMENT OF NUCLEAR ALKOXYL GROUPS BY THE ACTION OF GRIGNARD REAGENTS

REYNOLD C. FUSON, RUSSELL GAERTNER, AND DAVID H. CHADWICK¹*Received February 9, 1948*

It was discovered by Richtzenhain and Nippus that replacement of the 2-alkoxyl group in 2,3-dialkoxybenzonitriles could be effected by the action of Grignard reagents (1, 2). Efforts to bring about a similar replacement in 2-methoxy-1-naphthonitrile were unsuccessful, however (3). Subsequently attention has been directed to certain methoxybenzonitriles closely similar to the 2,3-dimethoxy derivative employed by Richtzenhain. 2-Methoxy- (I), 2,6-dimethoxy- (II), and 2,5-dimethoxybenzonitrile (III) were found to undergo no replacement of methoxyl groups.



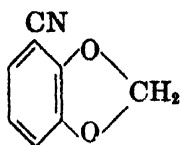
Under somewhat different conditions, Baker and Smith (4) obtained good yields of the expected dimethoxy ketones by the action of methyl and phenyl Grignard reagents on 2,3-dimethoxybenzonitrile (IV). It seemed possible, therefore, that our failure to effect replacement in similar compounds might have been due to a difference between our procedure and that of Richtzenhain. Accordingly, we attempted to repeat Richtzenhain's work with the ethyl and isopropyl Grignard reagents. Yields comparable with his were obtained only by decreasing the ratio of Grignard reagent to nitrile to 1.25:1. When isopropylmagnesium bromide was employed in this ratio, a yield of 83% of pure 2-isopropyl-3-methoxybenzonitrile was obtained. *t*-Butylmagnesium chloride, however, failed to effect replacement under these conditions. In fact, the only new examples of the replacement were realized with substituted 2,3-dimethoxybenzonitriles; namely, 2,3-dimethoxy-5-methylbenzonitrile (V) and a 2,3-dimethoxybromobenzonitrile (VI or VII).



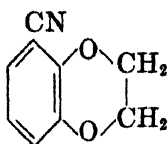
The results of these experiments led to the conclusion that replacement of an alkoxy group in the 2 position occurs only if the 3 position is occupied by a

¹ Present address: The Monsanto Chemical Company, Anniston, Alabama.

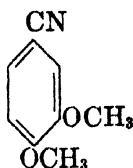
second alkoxy group. Attempts to effect replacement with 2,3-methylenedioxy- (VIII) and 2,3-ethylenedioxy-benzonitriles (IX) gave only 1,2-addition products. A similar result was obtained with veratronitrile (X) and piperonylnitrile (XI) in which replacement of the group in the 4 position might have been expected.



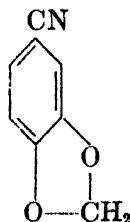
VIII



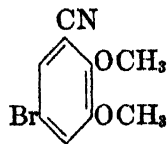
IX



X



XI



XII

In all of the replacements so far mentioned the alkoxy group involved is in a position *ortho* or *para* to a carbonyl or nitrile group and the reaction can, therefore, be represented as conjugate addition of the Grignard reagent followed by the loss of the elements of methanol. The conversion of 4,4'-dimethoxybiphenyl into a dimethoxy-*p*-terphenyl by the action of *p*-methoxyphenylmagnesium bromide by Price and Mueller (5) demonstrated, however, that a carbonyl or nitrile group is not necessary.

2,3-Dimethoxy-5-methylbenzonitrile (V), a new compound, was made from 2-methoxy-4-methylphenol. The phenol was converted by the Duff method, as modified by Liggett and Diehl (6), to 2-hydroxy-3-methoxy-5-methylbenzaldehyde, from which the nitrile was prepared by usual procedures.

The bromo compound (VI or VII) was formed by bromination of 2,3-dimethoxybenzonitrile (IV). In an attempt to identify the bromo compound, 2,3-dimethoxy-5-bromobenzonitrile (XII) was prepared; the two compounds proved to be unlike.

The ethylenedioxy compound (IX), also new, was synthesized from 2,3-dihydroxybenzoic acid by treatment with ethylene bromide followed by conversion of the ethylenedioxybenzoic acid to the nitrile.

EXPERIMENTAL²

Reaction of ethylmagnesium bromide with the benzonitriles. A. 2,6-Dimethoxybenzonitrile. The nitrile (12 g.) suspended in a mixture of 50 ml. of ether and 50 ml. of benzene was added in four approximately equal portions at fifteen-minute intervals to a Grignard reagent prepared from 3.5 g. of magnesium, 16 g. of ethyl bromide, and 100 ml. of ether. After the addition was completed the mixture was stirred for four hours at room temperature and overnight under reflux. The products were isolated by usual procedures. A small amount (0.8 g.) of unchanged 2,6-dimethoxybenzonitrile was recovered along with 11 g. of the crude imine of 2,6-dimethoxypropiophenone (m.p. 68–72°). The imine was characterized by transformation into the hydrochloride. The salt was dissolved in chloroform and precipitated by the addition of ether; m.p. 168–170°.

Anal. Calc'd for $C_{11}H_{14}ClNO_2$: C, 57.51; H, 7.02.

Found: C, 57.07; H, 7.29.

² Microanalyses were by Misses Theta Spoor and Betty Snyder.

B. 2-Methoxybenzonitrile. 2-Methoxybenzonitrile was prepared by a method similar to that employed by Clark and Read (7) for the synthesis of *o*-tolunitrile. When 16.6 g. of this nitrile was treated with ethylmagnesium bromide by a procedure similar to that outlined for 2,6-dimethoxybenzonitrile, the only product which could be identified was a yellow oil (13 g.) that proved to be the corresponding imine. Its hydrochloride melted at 157–158°.

Anal. Calc'd for $C_{10}H_{11}ClNO$: C, 60.14; H, 7.07.

Found: C, 59.98; H, 7.05.

C. 2,5-Dimethoxybenzonitrile. This nitrile, prepared by dehydration of the corresponding oxime, melted at 81–83° (8). When 10.5 g. of the nitrile was treated with ethylmagnesium bromide it yielded 9.5 g. of the imine of 2,5-dimethoxypropiophenone. The hydrochloride melted at 144–145°.

Anal. Calc'd for $C_{11}H_{13}ClNO_2$: C, 57.51; H, 7.02.

Found: C, 56.72; H, 7.25.

D. 2,3-Dimethoxybenzonitrile. When this nitrile (12 g.) was treated with ethylmagnesium bromide according to the directions of Richtzenhain (1) 3.5 g. of 2-ethyl-3-methoxybenzonitrile was obtained. The product after recrystallization from low-boiling petroleum ether, melted at 35–36°. It became liquid when mixed with 2,3-dimethoxybenzonitrile at room temperature.

Anal. Calc'd for $C_{10}H_{11}NO$: C, 74.50; H, 6.88.

Found: C, 74.76; H, 7.07.

*** Reaction of 2,3-dimethoxybenzonitrile with Grignard reagents.** A. *Ethylmagnesium bromide.* In view of the low yield obtained above, the ratio of Grignard reagent to nitrile was reduced. The following procedure was essentially that used in all subsequent reactions of nitriles with Grignard reagents, unless otherwise specified.

To a Grignard reagent prepared from 4.4 g. of magnesium turnings and 20 g. of ethyl bromide in 100 ml. of dry ether was added over a period of two hours a solution of 24 g. of the nitrile in 100 ml. of dry ether. After being stirred overnight at room temperature, the mixture was heated at reflux for four hours and cooled in an ice-bath; then it was poured into a mixture of ammonium chloride solution and ice. In the presence of ice, the ether layer was separated, washed with dilute sodium hydroxide solution, washed twice with saturated sodium chloride solution, and extracted repeatedly with dilute hydrochloric acid, the extracts being retained in an ice-bath for later neutralization and isolation of imines, if desired.

The ether layer was washed with ammonium chloride solution, and the nitriles isolated by usual procedures. Distillation of the crude product *in vacuo* at 92–95° (1 mm.) gave 14.4 g. (60% yield) of 2-ethyl-3-methoxybenzonitrile; m.p. 35–36°. A further decreased ratio was found to be unsatisfactory as was the use of a higher reflux temperature obtained by replacement of part of the ether by benzene.

B. Isopropylmagnesium bromide. When 12 g. of the nitrile was treated with this Grignard reagent according to the procedure described above, 10.5 g. (83% yield) of a colorless oil, b.p. 109–110° (1 mm.), n_D^{20} 1.5240, was obtained. Richtzenhain and Nippus (2) reported the boiling point 91–93° (0.2 mm.) for 2-isopropyl-3-methoxybenzonitrile of 95% purity, which they obtained from the same reactants in 81% yield.

Anal. Calc'd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48.

Found: C, 75.64; H, 7.18.

C. *t*-Butylmagnesium chloride. Treatment of 12 g. of the nitrile with this Grignard reagent gave 7.4 g. of starting material and 4.3 g. of an oily yellow imine. The crude product melted at 34.5–35.5°. *t*-Butyl 2,3-dimethoxyphenyl ketimine hydrochloride, a white powder, melted at 205.5–206° with decomposition after purification by repeated precipitation from chloroform with ether.

Anal. Calc'd for $C_{13}H_{20}ClNO_2$: C, 60.57; H, 7.82.

Found: C, 60.71; H, 7.87.

2,3-Dimethoxybromobenzonitrile. To a refluxing solution of 12 g. of 2,3-dimethoxybenzonitrile in 20 ml. of carbon tetrachloride (to which had been added small amounts of iron powder and iodine) was added slowly a solution of 12.8 g. of bromine in 10 ml. of the

solvent. When the evolution of hydrogen bromide appeared complete, conventional procedures for isolation gave 10.6 g. (59% yield) of white needles from methanol; m.p. 96–97°. A small amount was distilled *in vacuo*; b.p. 119–121° (1 mm.). Recrystallization from high-boiling petroleum ether gave white needles; m.p. 97.5–98.5°.

Anal. Calc'd for $C_9H_8BrNO_2$: C, 44.65; H, 3.33.

Found: C, 44.27; H, 3.40.

Reaction of 2,3-dimethoxybromobenzonitrile and ethylmagnesium bromide. A. When the above nitrile (15 g.) was treated with ethylmagnesium bromide according to the directions of Richtzenhain for 2,3-dimethoxybenzonitrile (1), the principal product was the imine portion, a dark viscous oil, weighing 10.9 g. Ethyl 2-ethyl-3-methoxybromophenyl ketimine hydrochloride was a light yellow powder sintering at 215° and melting at 226–228°, with decomposition.

Anal. Calc'd for $C_{12}H_{17}BrClNO$: C, 46.99; H, 5.59.

Found: C, 46.92; H, 5.50.

The nitrile fraction, a dark viscous oil, weighed 3 g. and deposited 0.39 g. of a solid which melted at 75–76° after recrystallization from low-boiling petroleum ether. It proved to be identical with the nitrile obtained in much better yield in the succeeding experiment.

B. Treatment of the nitrile (25 g.) with ethylmagnesium bromide in the reduced ratio described for 2,3-dimethoxybenzonitrile gave 7.7 g. of imines and, after recrystallization from high-boiling petroleum ether, 9.0 g. (36% yield) of 2-ethyl-3-methoxybromobenzonitrile melting at 70–72°. Further purification involved excessive loss. A sample was distilled; b.p. 125–126° (1 mm.). After careful recrystallization from the same solvent, large colorless crystals were obtained; m.p. 75.5–76.5°.

Anal. Calc'd for $C_{10}H_{10}BrNO$: C, 50.02; H, 4.19.

Found: C, 49.92; H, 4.13.

2-Hydroxy-3-methoxy-5-bromobenzaldehyde. This compound was prepared by bromination of *o*-vanillin in carbon disulfide at room temperature for two days. A 51% yield of a product melting at 128–129° was obtained after recrystallization from high-boiling petroleum ether. The compound had been prepared previously by Rupp and Linck (9) by bromination in acetic acid, a procedure which could not be repeated satisfactorily. They reported the melting point 127°.

2,3-Dimethoxy-5-bromobenzaldehyde. Methylation with methyl sulfate according to the method of Davies (10) gave an almost quantitative yield of dimethoxy compound melting at 79–81° after recrystallization from aqueous ethanol; the reported melting point was 81°.

2,3-Dimethoxy-5-bromobenzaldoxime. The oxime separated from aqueous ethanol in white needles; m.p. 132.5–133.0°. The yield was practically quantitative. The compound sublimed *in vacuo* at 100°.

Anal. Calc'd for $C_9H_9BrNO_2$: C, 41.56; H, 3.88.

Found: C, 41.62; H, 3.86.

2,3-Dimethoxy-5-bromobenzonitrile. A mixture of 7 g. of the crude oxime, 7 g. of anhydrous sodium acetate, and 30 ml. of acetic anhydride was heated at reflux for 3 hours, cooled slightly, and poured into 150 ml. of cold water with stirring. When cooled, the nitrile solidified. Its solution in high-boiling petroleum ether, after decolorization with Darco, deposited 5 g. (72% yield) of white needles; m.p. 93–94°. The compound sublimed *in vacuo* at 56°.

Anal. Calc'd for $C_9H_8BrNO_2$: C, 44.65; H, 3.33.

Found: C, 44.92; H, 3.34.

That this compound was different from the bromination product of 2,3-dimethoxybenzonitrile was shown by a mixture melting point determination. A mixture of the two compounds melted at 72–74°.

2-Hydroxy-3-methoxy-5-methylbenzaldehyde. The Duff reaction as modified by Liggett and Diehl (6) was applied to creosol. A further modification, found advantageous in this reaction, consisted of grinding the creosol (50 g.) with an equal weight of hexamethylenetetramine until a thick paste was obtained. This material, when allowed to stand overnight

in a thin layer, formed a dry solid. It was powdered and used in the modified procedure. The product of steam distillation of the reaction mixture was 24 g. (40% yield) of light yellow crystals; m.p. 75–77°. The melting point 77° has been reported (11) for the compound made by the usual Duff procedure.

2,3-Dimethoxy-5-methylbenzonitrile. 2,3-Dimethoxy-5-methylbenzaloxime (44 g.), prepared from the above material by successive methylation and treatment with hydroxylamine hydrochloride according to Manske and Ledingham (11), was converted to the nitrile by the method described for 2,3-dimethoxy-5-bromobenzonitrile. The addition of ice was necessary to bring about solidification of the crude product. Distillation *in vacuo* gave 32.6 g. (81.5% yield) of a colorless liquid, b.p. 128–130° (1 mm.), which solidified; m.p. 35–36°. Recrystallization of the solid from low-boiling petroleum ether gave needles; m.p. 36–37°.

Anal. Calc'd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26.

Found: C, 67.96; H, 6.43.

Reaction of 2,3-dimethoxy-5-methylbenzonitrile and ethylmagnesium bromide. Treatment of 12 g. of the distilled nitrile with the Grignard reagent in the usual way gave a neutral fraction weighing 8.1 g. and an imine portion weighing 4.0 g. The neutral portion was distilled *in vacuo* (1 mm.). The first fraction (6.3 g., b.p. 108–110°) solidified; m.p. 41–43°. The yield of 2-ethyl-3-methoxy-5-methylbenzonitrile was 52%. The nitrile separated from low-boiling petroleum ether in white needles; m.p. 42.5–43.5°.

Anal. Calc'd for $C_{11}H_{13}NO$: C, 75.39; H, 7.48.

Found: C, 75.31; H, 7.48.

The second fraction of the distillate (0.8 g., b.p. 113–116°) did not crystallize when seeded with either the above nitrile or the starting material. It was probably a ketone or mixture of ketones resulting from hydrolysis of imines before their separation from the reaction mixture.

The imine fraction failed to form a crystalline hydrochloride. It was hydrolyzed by brief warming with dilute hydrochloric acid, and the oily ketones were isolated by ether extraction. Two fractionations at reduced pressure gave 2.5 g. of a light yellow liquid boiling at 100–102° (1 mm.); n_D^{20} 1.5251. The forerun and residue were negligible. Analysis showed that the oil had a composition corresponding to a mixture of about equal parts of 2,3-dimethoxy-5-methylpropiophenone and 2-ethyl-3-methoxy-5-methylpropiophenone. Another attempt to fractionate this oil by distillation *in vacuo* gave no apparent separation.

Anal. Calc'd for $C_{12}H_{14}O_2$: C, 69.20; H, 7.75.

for $C_{13}H_{16}O_2$: C, 75.69; H, 8.80.

Found: C, 72.44; H, 8.14.

An attempt to form the oxime gave an oil which could not be induced to crystallize.

Reaction of piperonylnitrile and ethylmagnesium bromide. The Grignard reagent acted on 9.85 g. of the nitrile (12) in the usual manner to give 2.3 g. of practically pure starting material in the neutral fraction and 9.4 g. of solid yellow imine. The crude imine melted at 36–38° and gave a white hydrochloride; m.p. 143–144°. It proved too easily hydrolyzed to be analyzed, and 3 g. of the imine was accordingly converted to the ketone by treatment with warm acid. This compound weighed 2.5 g. and melted at 38–39°, the reported melting point of 3,4-methylenedioxypropiophenone (13). The phenylhydrazone, reported to melt at 97° (14), was prepared but melted at 106–107°. However, the melting points of the semicarbazone, m.p. 185–187°, and the oxime, m.p. 103–104°, agreed well with the reported values of 187–188° (15) and 104° (16), respectively.

Reaction of veratronitrile and ethylmagnesium bromide. Veratronitrile (10 g.) (17) and the Grignard reagent reacted in the usual fashion to form 5.2 g. of yellow imine; m.p. 55–57°, 2.7 g. of the nitrile being recovered. Treatment of the imine with hydrogen chloride gave a gummy precipitate, which, however, could be converted to the ketone by hydrolysis. Two grams of the imine yielded 1.1 g.; m.p. 58–59°, agreeing with the recorded melting point (60°) of 3,4-dimethoxypropiophenone (18). The phenylhydrazone melted at 107–109°. The value in the literature is 108–110° (18).

Reaction of 2,3-methylenedioxybenzonitrile and ethylmagnesium bromide. This nitrile (8.5 g.) (19) reacted with the Grignard reagent to give 1.4 g. of neutral material and 8.1 g. of an imine. The neutral material proved to be identical with the ketone described below. The imine, pressed free of oil, melted at 26–28°. It formed an easily hydrolyzed hydrochloride melting at about 330°, with decomposition. From 0.3 g. of the imine was obtained 0.2 g. of the ketone; m.p. 59–61° before purification. During distillation of a larger sample of this material an interesting transition was noted. At 135–140° (1 mm.) it distilled as a yellow oil which gradually formed thick transparent needles. When cooled they changed rapidly into a white opaque form; m.p. 59–61°. Recrystallization from a mixture of high- and low-boiling petroleum ethers gave white needles of 2,3-methylenedioxypropiofenone; m.p. 63.5–64.5°.

Anal. Calc'd for $C_{10}H_{10}O_2$: C, 67.40; H, 5.66.

Found: C, 67.83; H, 5.90.

2,3-Methylenedioxypropiofenone oxime, after recrystallization from dilute ethanol, formed white needles; m.p. 112–113°.

Anal. Calc'd for $C_{10}H_{11}NO_2$: C, 62.16; H, 5.74.

Found: C, 62.15; H, 6.02.

2,3-Ethylenedioxybenzoic acid. The procedure was similar to that employed by Perkin and Trikojus for the methylenedioxy compound (19). A mixture of 44 g. of 2,3-dihydroxybenzoic acid, 46.5 g. of potassium hydroxide, 23.7 ml. of ethylene bromide, 250 ml. of water, and 107 ml. of 95% ethanol was heated under reflux in an oxygen-free atmosphere for twenty hours. The mixture was poured into 1 liter of an ice-hydrochloric acid mixture, and the precipitated acid collected and dried. The crude acid weighed 19.5 g. (38% yield) and gave no blue color with ferric chloride solution, indicating the absence of appreciable amounts of the dihydroxy acid. Purification was attended by excessive loss. Recrystallization from dilute acetic acid gave small white crystals; m.p. 195.5–196.5°.

Anal. Calc'd for $C_8H_6O_4$: C, 60.01; H, 4.47.

Found: C, 59.86; H, 4.70.

2,3-Ethylenedioxybenzoyl chloride. This compound, prepared in nearly quantitative yield by use of pure thionyl chloride, boiled at 107–108° (1 mm.). Although carefully recrystallized from high-boiling petroleum ether which had been dried over sodium, the white needles (m.p. 69.5–70.5°) gave analytical results indicating partial hydrolysis.

Anal. Calc'd for $C_8H_7ClO_2$: C, 54.43; H, 3.55.

Found: C, 55.61; H, 3.73.

2,3-Ethylenedioxybenzamide. The crude acid (17 g.) was converted to the acid chloride as indicated above, and the chloride was distilled at reduced pressure and dissolved in 100 ml. of benzene. This solution was added during the course of an hour to 200 ml. of concentrated ammonia water cooled in an ice-bath. The amide precipitated and was collected on a filter. By concentrating the mother liquor and again cooling, a total of 13.0 g. (77% yield based on crude acid) was obtained. Efficient cooling during the reaction is essential. Recrystallization of the amide from a mixture of benzene and high-boiling petroleum ether gave white crystals; m.p. 133–134°.

Anal. Calc'd for $C_8H_9NO_2$: C, 60.29; H, 5.07.

Found: C, 60.43; H, 4.98.

2,3-Ethylenedioxybenzonitrile. The crude amide (13.4 g.) was heated under reflux with 50 ml. of purified thionyl chloride for six hours. After the excess reagent had been removed at the aspirator, 11.0 g. (91% yield) of the nitrile distilled at 127–129° (1 mm.) as a yellow oil. When recrystallized from a mixture of high- and low-boiling petroleum ethers, it formed white needles melting at 51.5–52°.

Anal. Calc'd for $C_8H_7NO_2$: C, 67.08; H, 4.38.

Found: C, 67.19; H, 4.21.

Reaction of 2,3-ethylenedioxybenzonitrile and ethylmagnesium bromide. The reaction of 8 g. of the nitrile with the Grignard reagent gave 5.3 g. of neutral material melting at 54–56° and 2.9 g. of an imine. The neutral fraction proved to be identical with the ketone de-

scribed below. No crystalline hydrochloride could be obtained from the imine but it was readily hydrolyzed to the ketone by warming with dilute acid. This compound melted at 55–56° without purification and distilled at 115–116° (1 mm.). 2,3-Ethylenedioxypropionophenone formed broad white needles from low-boiling petroleum ether; m.p. 57.5–58.0°.

Anal. Calc'd for $C_{11}H_{13}O_3$: C, 68.73; H, 6.30.

Found: C, 68.87; H, 6.32.

2,3-Ethylenedioxypropionophenone oxime was obtained in a form melting at 124–125° but changed on recrystallization from dilute ethanol to a more stable modification; m.p. 113–114°.

Anal. Calc'd for $C_{11}H_{13}NO_2$: C, 63.75; H, 6.33.

Found: C, 63.89; H, 6.36.

SUMMARY

Replacement of the 2-methoxyl group in 2-methoxybenzonitriles by the action of Grignard reagents has been observed only with those derivatives which have a second alkoxy group in position 3. Two new examples have been discovered.

The reaction of ethylmagnesium bromide with 2-methoxybenzonitrile, 2,5-dimethoxybenzonitrile, 2,6-dimethoxybenzonitrile, veratronitrile, piperonylnitrile, 2,3-methylenedioxybenzonitrile, and 2,3-ethylenedioxybenzonitrile has been found to produce only 1,2 addition products as contrasted to the formation of 2-ethyl-3-methoxybenzonitrile from 2,3-dimethoxybenzonitrile.

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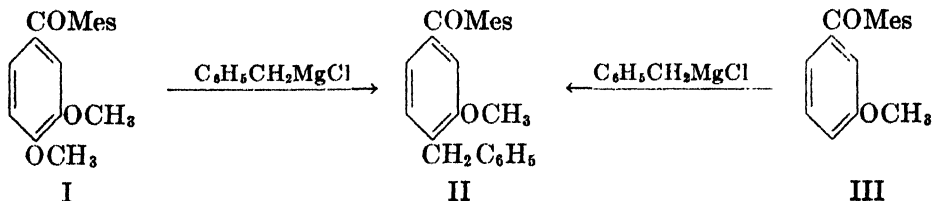
REPLACEMENT OF METHOXYL GROUPS IN *p*-METHOXYARYL KETONES BY THE ACTION OF THE GRIGNARD REAGENT

REYNOLD C. FUSON AND RUSSELL GAERTNER

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The introduction by means of the Grignard reagents of an alkyl or aryl radical into the *ortho* position of benzoylmesitylene and certain similarly constituted aryl ketones (1) was found to occur more readily with the corresponding *o*-methoxyl ketones (2). It seemed probable that alkylation in the *para* position, observed with benzyl, *t*-butyl (3), and methyl (4) Grignard reagents, would likewise proceed more readily with the corresponding *p*-methoxyaryl ketones. However, early attempts to convert anisyl duryl ketone to *p*-benzylphenyl duryl ketone by the action of benzylmagnesium chloride were not successful. The hope of achieving this type of reaction was revived when it was found that similar replacements of *ortho* alkoxy groups in the benzonitrile series were made possible by the presence of a second alkoxy group on the adjoining carbon atom (5).

This suggestion has proved fruitful. When 3,4-dimethoxyphenyl mesityl ketone (I) was treated with benzylmagnesium chloride, the methoxyl group in the 4 position was replaced by benzyl. The structure of the product, 3-methoxy-4-benzylphenyl mesityl ketone (II) was established by an independent synthesis. 3-Methoxyphenyl mesityl ketone (III) was found to react with benzylmagnesium chloride to undergo benzylation in the same manner as benzoyldurene (3).

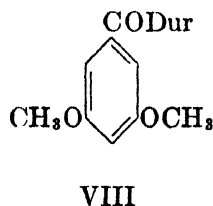
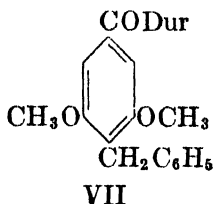
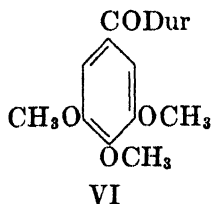


Phenylmagnesium bromide appeared to act on 3,4-dimethoxyphenyl mesityl ketone in a similar manner, but no proof of structure has been obtained for the product, presumed to be 4-mesityl-2-methoxybiphenyl.

Similar results were obtained with 3,4-dimethoxyphenyl duryl ketone (IV), the methoxyl group in the 4 position being replaced by a benzyl group. The product (V) was obtained also by treatment of 3-methoxyphenyl duryl ketone with benzylmagnesium chloride.



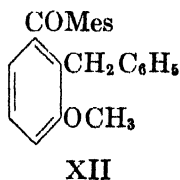
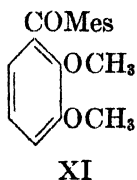
Another interesting example of this replacement was observed when 3,4,5-trimethoxyphenyl duryl ketone (VI) was treated with benzylmagnesium chloride. The product, 3,5-dimethoxy-4-benzylphenyl duryl ketone (VII), was identical with the benzylation product from 3,5-dimethoxyphenyl duryl ketone (VIII). The yield (58%) in the replacement reaction indicates that the promoting effect of the *ortho* methoxyl group is additive.



Renewed attempts to effect replacement of methoxyl groups in anisyl mesityl ketone (IX) and anisyl duryl ketone (X) have been unsuccessful. Rather, the formation of dihydro compounds of unknown structure was observed.



The relation of the second methoxyl group to the replacement of a methoxyl *ortho* to a hindered carbonyl group has also been investigated. 2,3-Dimethoxyphenyl mesityl ketone (XI), when treated with benzylmagnesium chloride, yielded 2-benzyl-3-methoxyphenyl mesityl ketone (XII). However, the low yield in this reaction compared to the yields previously reported (2) indicates that the effect of the second methoxyl group is not important in this case.



EXPERIMENTAL¹

3,4-Dimethoxyphenyl mesityl ketone. A solution of 16 g. of veratroyl chloride (6) in 80 ml. of carbon disulfide was added with mechanical stirring to a mixture of 9.9 g. of mesitylene, 11.4 g. of anhydrous aluminum chloride, and 40 ml. of the solvent over a period of 45 minutes and stirring continued for a like period. The mixture was decomposed with cold dilute hydrochloric acid, and the solvent layer was washed with water and 10% sodium hydroxide solution. The solvent was removed by distillation; there was obtained, after recrystalliza-

¹ Microanalyses were by Misses Theta Spoor, Betty Snyder, and Jane Wood and the Clark Microanalytical Laboratories, Urbana, Illinois. Melting points are corrected.

tion of the residue from ethanol, 14 g. (62% yield) of the ketone; m.p. 100–102°. It separated from high-boiling petroleum ether in white needles; m.p. 105–105.5°.

Anal. Calc'd for $C_{15}H_{20}O_2$: C, 76.03; H, 7.09.

Found: C, 76.23; H, 7.23.

Reaction of 3,4-dimethoxyphenyl mesityl ketone with Grignard reagents. A. Benzylmagnesium chloride. To a Grignard reagent prepared from 8.9 g. of benzyl chloride and 1.7 g. of magnesium turnings in 50 ml. of dry ether was added over a period of an hour a solution of 8 g. of the ketone in 65 ml. of ether and 10 ml. of benzene. Addition was accompanied by the formation of a red coloration changing to brown, a slight warming, and finally the separation of a tan precipitate. After being stirred for another hour, the reaction mixture was decomposed with cold dilute hydrochloric acid. Usual procedures yielded 11.4 g. of a light yellow gum; it was dissolved in methanol and the solution deposited 2.1 g. (22% yield) of yellow crystals; m.p. 90.5–92.5°. 3-Methoxy-4-benzylphenyl mesityl ketone separated from methanol in fine white needles; m.p. 93.5–94.5°; b.p. 205–210° (1 mm.).

Anal. Calc'd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02.

Found: C, 83.70; H, 7.25.

B. Phenylmagnesium bromide. Treatment of 12 g. of the ketone with this Grignard reagent as described above yielded 14 g. of a dark red gum. Distillation of this material *in vacuo* gave 10.2 g. of a light yellow gum; b.p. 200–210° (1 mm.). It could not be induced to crystallize, but three redistillations gave a light yellow gum which had the composition of 4-mesityl-2-methoxybiphenyl. The yield was 15% based on the yield of the bromination product described below.

Anal. Calc'd for $C_{22}H_{22}O_2$: C, 83.60; H, 6.71.

Found: C, 83.36; H, 6.93.

When 2 g. of this gum was treated with 1.08 g. of bromine in 20 ml. of carbon tetrachloride for 4 hours, there was isolated 0.5 g. of a solid which was recrystallized from methanol. White crystals having the composition of a monobromo derivative were obtained; m.p. 110.5–112°.

Anal. Calc'd for $C_{22}H_{21}BrO_2$: C, 67.48; H, 5.17.

Found: C, 67.49; H, 5.08.

Independent synthesis of 3-methoxy-4-benzylphenyl mesityl ketone. *m*-Methoxyphenyl mesityl ketone (5 g.) (2) was treated with benzylmagnesium chloride and the mixture heated under reflux for 2 hours. The resulting 7.7 g. of yellow oil was dissolved in methanol; the solution deposited 0.6 g. (9% yield) of clumped needles; m.p. 92.5–93.5° after recrystallization from methanol. The melting point was not depressed when this material was mixed with that previously isolated from the reaction of 3,4-dimethoxyphenyl mesityl ketone with benzylmagnesium chloride.

3,4-Dimethoxyphenyl duryl ketone. This ketone was prepared in 29% yield by a procedure similar to that described for 3,4-dimethoxyphenyl mesityl ketone. The ketone formed fine white needles after repeated recrystallization from a mixture of ethanol and benzene; m.p. 157.5–159°.

Anal. Calc'd for $C_{19}H_{22}O_2$: C, 76.48; H, 7.43.

Found: C, 76.40; H, 7.45.

Reaction of 3,4-dimethoxyphenyl duryl ketone and benzylmagnesium chloride. Treatment of 3.9 g. of the ketone with this Grignard reagent yielded 6.6 g. of a residual oil, which deposited 2 g. (42% yield) of yellow sandlike crystals from methanol. On being recrystallized repeatedly from ethanol-benzene, 3-methoxy-4-benzylphenyl duryl ketone formed white crystals; m.p. 187–188.5°.

Anal. Calc'd for $C_{25}H_{26}O_2$: C, 83.76; H, 7.31.

Found: C, 83.77, 84.01; H, 7.16, 6.87.

Independent synthesis of 3-methoxy-4-benzylphenyl duryl ketone. *m*-Methoxyphenyl duryl ketone. This ketone was prepared in 87% yield from *m*-methoxybenzoyl chloride (7)

and durene by the Friedel-Crafts method. It boiled at 182–184° (3 mm.) and separated from methanol in fine white needles; m.p. 127–127.5°.

Anal. Calc'd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51.

Found: C, 80.62; H, 7.51.

Reaction of m-methoxyphenyl duryl ketone and benzylmagnesium chloride. Ten grams of the ketone was treated with the Grignard reagent, the reaction mixture changing from purple to brown during the course of the addition and a 2-hour reflux period. There was obtained 4.6 g. (34% yield) of 3-methoxy-4-benzylphenyl duryl ketone by dissolving the resulting oil in methanol. One recrystallization from ethanol-benzene gave crystals melting at 185.5–187° and a mixture with the product obtained from 3,4-dimethoxyphenyl duryl ketone melted at 186.5–188°.

3,4,5-Trimethoxyphenyl duryl ketone. A solution of 29 g. of 3,4,5-trimethoxybenzoyl chloride (8) in 100 ml. of benzene was added over a period of 30 minutes to a reagent prepared from 27.7 g. of bromodurene, 3 ml. of ethyl bromide, and 3.25 g. of magnesium in 150 ml. of ether. After being stirred for an additional 15 minutes, the reaction yielded 6.8 g. (16%) of white crystals from methanol; m.p. 135–139°. The ketone was recrystallized from ethanol; m.p. 141.5–142°.

Anal. Calc'd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37.

Found: C, 73.41; H, 7.33.

Reaction of 3,4,5-trimethoxyphenyl duryl ketone and benzylmagnesium chloride. Addition of a solution of 6 g. of the ketone to the Grignard reagent caused formation of a green color, and finally a light colored solid separated. After stirring the reaction mixture for 45 minutes and decomposing, there was obtained from methanol solution 4.1 g. (58% yield) of crystals; m.p. 125–128°. 3,5-Dimethoxy-4-benzylphenyl duryl ketone separated from ethanol in long, colorless needles; m.p. 139–139.5°.

Anal. Calc'd for $C_{20}H_{22}O_3$: C, 80.38; H, 7.26.

Found: C, 80.29, 80.43; H, 7.29, 7.39.

Independent synthesis of 3,5-dimethoxy-4-benzylphenyl duryl ketone. 3,5-Dimethoxyphenyl duryl ketone. This compound was prepared in 21% yield by the Friedel-Crafts method employing 3,5-dimethoxybenzoyl chloride (9). The ketone separated from methanol in light yellow plates; m.p. 101.5–102°.

Anal. Calc'd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43.

Found: C, 76.58; H, 7.54.

Reaction of 3,5-dimethoxyphenyl duryl ketone and benzylmagnesium chloride. The ketone (2.4 g.) was treated with the benzyl Grignard reagent, giving a brown solution which precipitated a solid when heated under reflux for 90 minutes. From methanol there was obtained 0.74 g. (24% yield) of white crystals; m.p. 124–133°. The compound separated from ethanol in needles; m.p. 138–139°. The mixture melting point with the product obtained from 3,4,5-trimethoxyphenyl duryl ketone showed no depression.

*Anisyl mesityl ketone.*² A solution of *p*-methoxyphenylmagnesium bromide, prepared from 13 g. of magnesium, 72 g. of *p*-bromoanisole, and 200 ml. of dry ether, was added slowly, with stirring, to a solution of 59 g. of mesitoyl chloride in 200 ml. of dry ether. The mixture was decomposed with hydrochloric acid and the ether layer was washed with dilute sodium hydroxide solution. Evaporation of the solvent left the anisyl mesityl ketone as a solid. It was recrystallized from ethanol; m.p. 78°; yield 28 g.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.29; H, 7.10.

Found: C, 80.37; H, 7.31.

Reaction of anisyl mesityl ketone and benzylmagnesium chloride. The ketone (10 g.), when treated with this Grignard reagent, turned red-brown and yielded 16.2 g. of a light yellow gum which was dissolved in methanol. The solution deposited 2.7 g. (20% yield) of bright yellow crystals which were decolorized by distillation at reduced pressure; b.p. 194–200°

² This experiment was carried out by Dr. S. B. Speck.

(1 mm.). The compound, presumably 2-benzyl-4-methoxy-1,2-dihydrophenyl mesityl ketone, separated from methanol in flat white needles; m.p. 119.5–120.5°.

Anal. Calc'd for $C_{24}H_{20}O_2$: C, 83.20; H, 7.56.

Found: C, 83.48, 83.38; H, 7.68, 7.45.

The compound decolorized a solution of bromine in carbon tetrachloride, evolving hydrogen bromide, and reacted with a 0.5% solution of potassium permanganate in water and acetone. An attempted dehydrogenation over palladium on charcoal catalyst gave no crystalline substance.

Reaction of anisyl duryl ketone and benzylmagnesium chloride. On treatment of 10 g. of the ketone (4) with the benzyl Grignard reagent, warming occurred with the formation of a purple color turning to brown. Stirring was continued for an hour at room temperature. An amber gum (14.1 g.) was isolated and dissolved in methanol, the solution depositing 0.28 g. of a deep yellow powder; m.p. 222–226°. It was insoluble in the usual solvents and was recrystallized from diphenyl ether; m.p. 234.5–237°. The compound had the composition of 2-benzyl-4-methoxy-1,2-dihydrophenyl duryl ketone and reacted with a solution of potassium permanganate in acetone and water.

Anal. Calc'd for $C_{25}H_{20}O_2$: C, 83.29; H, 7.83.

Found: C, 83.01; H, 7.19.

2,3-Dimethoxyphenyl mesityl ketone. This ketone was prepared in 26% yield by the Friedel-Crafts method from *o*-veratroyl chloride (10). It was obtained in light yellow needles from methanol; m.p. 121.5–122°.

Anal. Calc'd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09.

Found: C, 75.69; H, 6.99.

Reaction of 2,3-dimethoxyphenyl mesityl ketone and benzylmagnesium chloride. The ketone (4.5 g.) in ethereal solution was added to the Grignard reagent, causing moderate warming and a red coloration. After stirring the reaction mixture at room temperature for 90 minutes, a light-colored precipitate had formed. A yellow oil (7.6 g.) was isolated and distilled at reduced pressure giving 3.3 g. of a light yellow gum; b.p. 150–190° (1 mm.). From methanol solution it deposited 0.38 g. (7% yield) of sandlike crystals; m.p. 102–106°. Repeated recrystallization of the compound, presumably 2-benzyl-3-methoxyphenyl mesityl ketone, from methanol gave white crystals; m.p. 111.5–112°.

Anal. Calc'd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02.

Found: C, 83.91, 83.85; H, 7.37, 7.12.

*Condensation of 2,3,5,6-tetramethylbenzoyl chloride with *o*-methoxyphenylmagnesium bromide.*³ A filtered solution of the Grignard reagent prepared from 26 g. of *o*-bromoanisole was added dropwise to a solution of 30 g. of 2,3,5,6-tetramethylbenzoyl chloride in 350 ml. of dry ether. The mixture was stirred at room temperature for one hour and decomposed with dilute hydrochloric acid. The ether layer was washed with 5% potassium carbonate solution and with water. Sodium 2,3,5,6-tetramethylbenzoate is insoluble in water. Acidification of the potassium carbonate solution yielded 7.0 g. of 2,3,5,6-tetramethylbenzoic acid. The solvent was distilled from the organic layer and ethanol added to the oily residue. The 2'-(*o*-methoxyphenyl)-2,3,5,6-tetramethylbenzophenone weighed 10.4 g. and, after recrystallization from a mixture of benzene and ethanol, melted at 153–154°.

Anal. Calc'd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02; mol. wt., 344.

Found: C, 83.90; H, 7.13; mol. wt. (ebullioscopic in chloroform), 320, 308.

From the original ethanol filtrate was obtained 16 g. of a solid which, after repeated recrystallization from ethanol, melted at 110–120°. It was probably impure *o*-methoxyphenyl duryl ketone.

*4'-Benzyl-2'-(*o*-methoxyphenyl)-2,3,5,6-tetramethylbenzophenone.*³ A Grignard reagent was prepared from 13 g. of benzyl chloride and 2.5 g. of magnesium, and to it was added 4.2 g. of 2'-(*o*-methoxyphenyl)-2,3,5,6-tetramethylbenzophenone. The deep red solution was heated under reflux for 11 hours and decomposed in the usual way. Distillation of the

³ This experiment was carried out by Dr. B. C. McKusick.

product yielded an oil and a tarry residue. Treatment of the tar with ether left 0.20 g. of needles which, after recrystallization from a mixture of ethanol and benzene, melted at 165.5–166.5°.

Anal. Calc'd for $C_{31}H_{30}O_2$: C, 85.68; H, 6.96.

Found: C, 85.97; H, 7.29.

SUMMARY

Replacement of a methoxyl group *para* to a hindered carbonyl group by the radical of a Grignard reagent has been achieved in three instances in which the *para* methoxyl group was flanked by one or more other methoxyl groups. Thus 3,4-dimethoxyphenyl mesityl ketone, 3,4-dimethoxyphenyl duryl ketone, and 3,4,5-trimethoxyphenyl duryl ketone, when treated with benzylmagnesium chloride, yielded respectively 3-methoxy-4-benzylphenyl mesityl ketone, 3-methoxy-4-benzylphenyl duryl ketone, and 3,5-dimethoxy-4-benzylphenyl duryl ketone.

Replacement of the methoxyl group in anisyl mesityl ketone and anisyl duryl ketone in a similar manner has not been realized.

URBANA, ILL.

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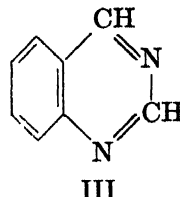
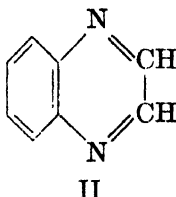
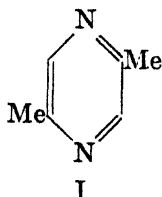
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CONDITIONS OF SALT FORMATION IN POLYAMINES AND KINDRED COMPOUNDS. SALT FORMATION IN THE TERTIARY 2-PYRIDYLAMINES, PHOSPHINES AND ARSINES

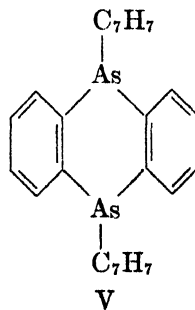
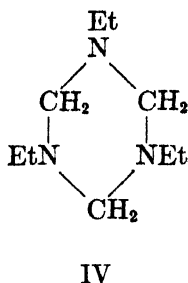
FREDERICK GEORGE MANN AND JAMES WATSON

Received February 10, 1948

It is well recognized that if in an organic molecule there are two or more amine groups, which by virtue of their nature and bonding should possess the normal basic properties of such groups, their mutual proximity may prevent these groups showing simultaneously these basic properties; for example, they may not all form salts even with strong acids, nor, if they are tertiary amine groups, may they all form quaternary salts. This inhibition of complete quaternary salt formation also applies to molecules containing more than one tertiary phosphine or arsine group. As examples of this phenomenon, both pyrazine (I) and 2,5-dimethylpyrazine form only a monohydrochloride and monomethiodide (1), quinoxaline (II) behaves similarly (2), and quinazoline (III) even when heated with an excess of



methyl iodide at 100° gives only a monomethiodide on the 3-nitrogen atom (3). Triethyltrimethylenetriamine (IV) forms only a monoethiodide (4). In the arsenic field, Chatt and Mann (5) have shown that each of the geometrically isomeric 5,10-di-*p*-tolyl-5,10-dihydroarsanthrenes (V) forms only a monomethiodide. Very many similar examples could be quoted.



To explain this phenomenon, Mann *et al.* (5, 6) have pointed out, that when in such molecules the first nitrogen or arsenic atom forms a salt, the positive pole thus produced on the nitrogen or arsenic atom has a very strong inductive effect, particularly in quaternary salts (7, 8), and that this inductive effect towards the positive pole will tend to draw electrons away from a neighboring nitrogen or arsenic atom; this electronic drag from these latter atoms will reduce the activity

of the lone pair of electrons on these atoms, and their normal salt-forming properties may thus be reduced or even entirely suppressed. In suitable polyamines this deactivating effect on one nitrogen atom may be reinforced by salt formation on two or more neighboring amine groups.

If these theoretical considerations are correct, the deactivating influence caused by the inductive effect can operate only between two atoms which are in comparatively close proximity, if they are linked by a saturated chain; in such cases the effect *must* fall off rapidly as the distance between the two atoms is increased. Considerable support for the theory arises therefore from the work of Mann and Pope (9), who showed that tri-2-aminoethylamine, $N(CH_2CH_2NH_2)_3$, gave a tetrahydrochloride from cold concentrated hydrochloric acid, but that this salt on exposure to the air spontaneously lost one molecule of hydrochloric acid and gave the trihydrochloride (VI); on the other hand, tri-3-aminopropylamine gave an extremely stable tetrahydrochloride (VII).



VI



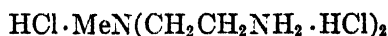
VII

It is thus evident that in the trihydrochloride (VI), the combined influence of the positive poles on the three primary amine groups so weakens the reactivity of the tertiary nitrogen atom that it can show its normal basic properties only in the presence of strong acids; in the tetrahydrochloride (VII) however, this combined influence of the three primary amine salt groups is now too distant to affect appreciably the basic properties of the tertiary nitrogen atom, which therefore itself forms stable salts.

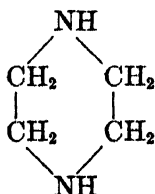
It is noteworthy that di-2-aminoethylamine and di-2-aminoethylmethylaniline form the stable trihydrochlorides (VIII) and (IX) respectively (10).



VIII



IX

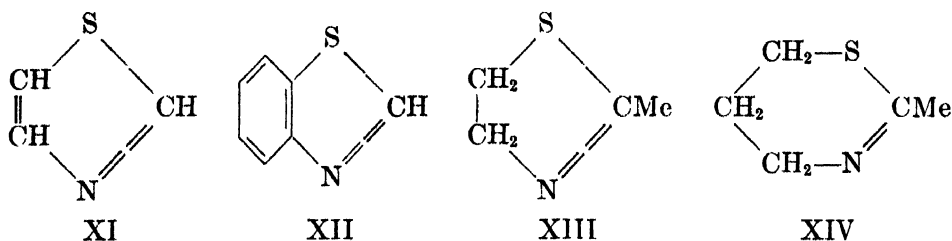


This is precisely what one would expect; if the combined effect of the three positive poles in the trihydrochloride (VI) is to weaken but not entirely suppress the activity of the "central" nitrogen atom in this compound, that of the two positive poles on the primary amine salt groups in VIII and IX will not seriously impair the basic properties of the remaining nitrogen atom in the presence of a strong acid. Other examples of this cumulative effect arise in our present work.

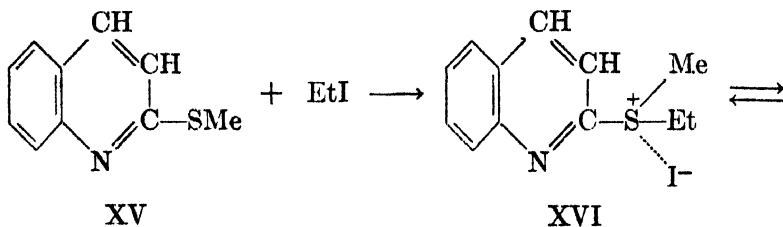
In contrast to the behavior of pyrazine (I), it should be noted that piperazine (X) gives a dihydrochloride (11), and N,N-dimethylpiperazine gives both

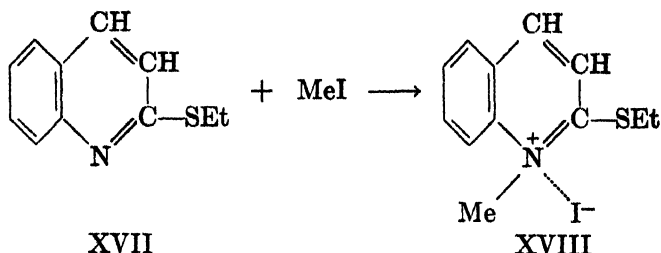
a dihydrochloride and a dimethiodide (12). It is clear therefore that when two nitrogen atoms are linked by a suitable conjugated chain as in the pyrazine (I), the electronic attraction exerted by the positive pole on one nitrogen (in the monohydrochloride) is readily transmitted by the mesomeric effect through this chain, and the second nitrogen atom is thus strongly affected. When, however, the chain is saturated, the electronic attraction is necessarily carried solely by the inductive effect and is (as would be expected) much weaker when transmitted an equivalent distance. Hence, in the piperazine molecules the second nitrogen atom is not detectably affected by the charge on the first nitrogen atom, and in the saturated aliphatic polyamine (VI) the cumulative effect of three positive poles is required to transmit effectively the deactivating influence over this distance.

This deactivating effect by positive poles is not limited to compounds of the Group V B elements, although it appears most strongly in such compounds. It is known that thiazole (XI) and its 2-methyl and 2,4-dimethyl derivatives and also benzothiazole (XII) when heated with an excess of methyl iodide form only monomethiodides (13), the methyl iodide adding solely to the nitrogen. It might be objected that the sulfur atom in these compounds has however, much of the "semi-aromatic" inactivity of the sulfur atom in thiophene, and would therefore be unlikely to form a sulfonium salt. Nevertheless, the same condition of monomethiodide formation applies also to, for example, 2-methylthiazoline (XIII) and to 2-methyldihydro-1,3-thiazine (XIV) (14, 15, 18), to which the above objection cannot apply.



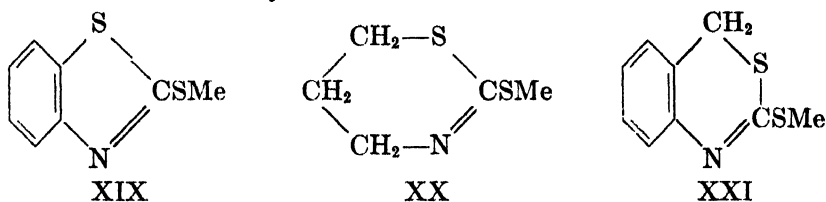
Valuable confirmation of our theoretical considerations also arises in the work of Beilenson and Hamer (16), who showed that 2-methylthioquinoline (XV), when heated with methyl iodide at 100° for 24 hours, formed only a monomethiodide, the position of the methyl group on the nitrogen atom being proved. When however, 2-methylthioquinoline (XV) was similarly treated with ethyl iodide, 2-ethylthioquinoline methiodide (XVIII) was formed.





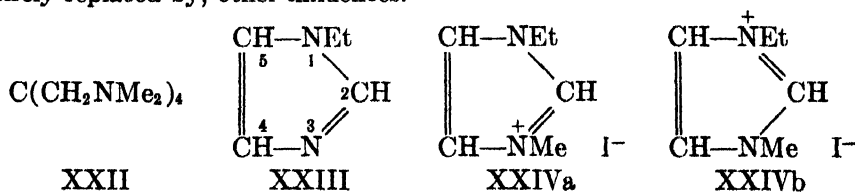
The only probable mechanism for this transformation is that the initial attack of the ethyl iodide is on to the aliphatic sulfur atom of the 2-methylthioquinoline (XV) to give the sulfonium salt (XVI). The latter then dissociates to give 2-ethylthioquinoline (XVII) and methyl iodide. It is almost certain that this dissociation is reversible (since such dissociation-equilibria are commonly encountered in the alkyl sulfonium halides), but the highly reactive methyl iodide thus liberated also combines with the nitrogen atom to give the quaternary ammonium salt (XVIII). The positive pole on this nitrogen (being more powerful than that on a sulfonium group) immediately deactivates the divalent sulfur atom in XVIII, and consequently the ultimate reaction is entirely in favor of this salt.

This is not an isolated example. It has been shown (17, 18) that 2-methylthiobenzothiazole (XIX), 2-methylthiodihydro-1,3-thiazine (XX) and 3-methylthio-2,4-benzothiazine (XXI), when heated with methyl iodide, give only quaternary monomethiodides, but with ethyl iodide again give the quaternary monomethiodide of the ethylthio derivatives.



In all these four types of compound, therefore, initial attack by the alkyl halide must be on the aliphatic sulfur atom, and the instability of the sulfonium salt then allows attack at the nitrogen atom, with consequent inactivation of the sulfur.

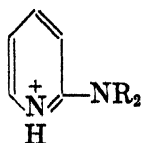
The phenomenon of inductive deactivation which we have briefly outlined above is so widely spread and occurs in such a variety of compounds that other influences must often come into play. We do not suggest that our theory of inactivation by the inductive effect of neighboring groups represents the only effect which is present in such molecules: this effect may be blended with, or even entirely replaced by, other influences.



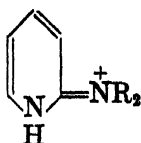
For example, it has been shown by Mann *et al.* (19, 6) that tetrakis-dimethylaminomethylmethane (XXII) forms a stable tetrahydrochloride, but when heated with an excess of methyl, ethyl, allyl, or benzyl iodide forms only a diquaternary salt; the dimethiodide when heated to its decomposition point will, however, give a small yield of the tetramethiodide, a reaction which is not shown by the other three diquaternary salts. The existence of the stable tetrahydrochloride shows clearly that in spite of the close proximity of the four tertiary nitrogen atoms, the cumulative effect of the positive poles is not sufficient to deactivate any one of these nitrogen atoms. Consequently one would not expect the inductive effect to prevent the formation of the tetramethiodide under normal conditions of quaternary salt formation. In this case, therefore, steric effects probably play a major part; protons can readily add on to the four amine groups in the tetramine (XXII), but the tetrahedral arrangement of these groups around the central carbon atom makes the ingress of methyl (or other alkyl) groups increasingly difficult for spatial reasons, and hence only the dimethiodide is normally formed. The violent conditions of thermal decomposition are required to force four methyl groups on to the tetramine, and even this method fails with larger alkyl groups. The use of Stuart models confirms this steric argument.

Yet another factor probably enters into the behavior of 1-ethyliminazole (XXIII), which when heated with an excess of methyl iodide gives only the 3-methiodide (XXIVa), the N-ethyl group refusing to unite with a second methyl iodide molecule (20). It will be seen however that the cation in XXIVa produced by the initial addition of methyl iodide is at once stabilized by resonance hybrid formation with the cation XXIVb; hence each nitrogen atom is partly tertiary and partly quaternary, and this effect again probably predominates over any inductive effect, which can of course exist only in the separate canonical forms.

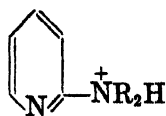
One further example of inactivation by a neighboring polar group may be cited, because it is closely connected to our present work. 2-Aminopyridine, 2-monoalkylaminopyridines, and 2-dialkylaminopyridines all act as monoacidic bases, forming for example monohydrochlorides and monopicrates (21). The position of proton attack in this salt formation is uncertain, but it is probably onto the pyridyl nitrogen, as the cation thus formed would be stabilized by resonance hybrid formation between XXVa and XXVb ($R = H$ or alkyl), whereas the cation formed by proton attack at the side chain (XXVI) lacks this stabilizing factor.



XXVa



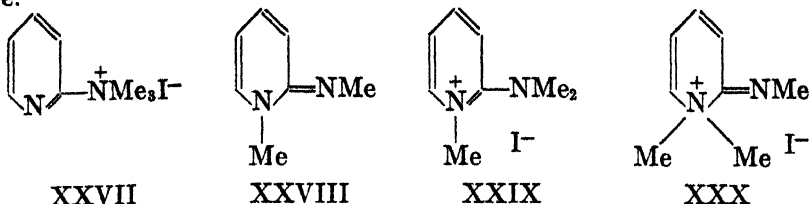
XXVb



XXVI

Nevertheless, it is known that 2-dimethylaminopyridine reacts even with an excess of methyl iodide at 100° to give the compound XXVII (22), the attack at

the side chain recalling the initial behavior of the methylthiol compounds cited above.

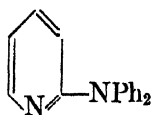


The constitution of XXVII is known, because cold methyl iodide reacts readily with 1-methyl-2-methylimino-1,2-dihydropyridine (XXVIII) to give a salt which with silver oxide or caustic alkali yields dimethylamine and N-methyl-2-pyridone. Hence this salt must be XXIX and not XXX, and since it is isomeric with the compound XXVII, the latter must have the structure stated. Here again the cation of the salt XXIX should be stabilized by resonance of precisely the same type as that given above between XXVa and XXVb. The fact that in spite of this stabilizing influence this compound is not formed by the action of methyl iodide on 2-dimethylaminopyridine must apparently be due to the tertiary nitrogen in the side chain of the latter compound having greater reactivity than the pyridyl nitrogen group; hence when stable quaternary salt formation occurs on the side chain, the pyridyl nitrogen atom immediately becomes inactivated. Consideration of structures XXVII and XXIX confirms the experimental fact that steric hindrance is not a controlling factor in the formation of either compound. In all these 2-aminopyridine derivatives, however, the deactivation of one amino group by a positive pole on the other group is particularly striking.

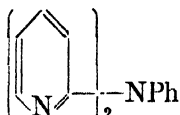
It will be clear that an inductive effect arising from a cause other than a full positively charged pole may also tend to produce the above deactivation. For example, phenyldiethylarsine, $C_6H_5As(C_2H_5)_2$, undergoes ready atmospheric oxidation to the arsine oxide, whereas phenyl-bis(2-cyanoethyl)arsine, $C_6H_5As(C_2H_4CN)_2$, when molten or in solution, is not perceptibly affected by exposure to air; nevertheless, the latter compound combines with methyl iodide on warming to give the methylarsonium iodide, $[C_6H_5(CH_3)As(C_2H_4CN)_2]I$. The positive inductive effect of the cyano groups has thus reduced but not suppressed the reactivity of the tertiary arsenic atom. A similar reduction in the activity of the tertiary arsenic atom occurs also in the amidine salts and the carboxylic acids derived from 2-cyanoethylarsines of the above type (40). As a further example, azobenzene can be readily oxidized to azoxybenzene, $C_6H_5NO:NC_6H_5$, but a similar oxidation of the second nitrogen cannot be accomplished, and compounds of the type $C_6H_5NO:NOC_6H_5$ are unknown, although there is apparently no steric obstruction to their formation, particularly in the *trans* form. There is little doubt, therefore, that in azoxybenzene the strong inductive effect from the first nitrogen atom to the contiguous oxygen atom completely inactivates the second nitrogen atom. The same factor may be responsible for the apparent

non-existence of disulfoxides of type $R \cdot SO \cdot SO \cdot R$, the many compounds to which this structure had initially been allocated having been shown later to be sulfone-sulfides of type $R \cdot SO_2 \cdot SR$ (41).

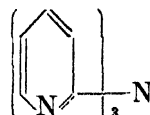
In the course of a chemotherapeutic investigation carried out in the second half of World War II, we had occasion to prepare the complete series of tertiary amines, phosphines, and arsines which systematically would arise from the step-by-step replacement of the phenyl groups in triphenyl-amine, -phosphine, and -arsine by 2-pyridyl groups. Thus, mono-2-pyridyldiphenylamine (XXXI), originally obtained by Tschitschibabin (21), was prepared by the interaction of 2-bromopyridine and diphenylamine in the presence of potassium carbonate and copper powder. Mono-2-pyridyldiphenyl-phosphine and -arsine were prepared by the action of magnesium-2-pyridyl bromide on diphenylmonochloro-phosphine and -arsine respectively. Di-2-pyridylmonophenylamine (XXXII) was prepared by the interaction of 2-bromopyridine and aniline [Wibaut and Tilman (23)], and the corresponding phosphine and arsine by the action of magnesium-2-pyridyl bromide on phenyldichloro-phosphine and -arsine in turn. Finally



XXXI



XXXII



XXXIII

tri-2-pyridylamine (XXXIII) was prepared by the interaction of 2-bromopyridine and 2-aminopyridine [Wibaut and La Bastide (24)], and tri-2-pyridyl-phosphine and -arsine by the action of an excess of the above Grignard reagent on phosphorus trichloride and arsenic trichloride respectively [Davies and Mann (25)].

Quite apart from chemotherapeutic properties, however, these nine compounds form a unique series for the comparative study of salt formation, for in each compound there is a theoretical possibility of quaternary salt formation on the "central atom" (*i.e.*, nitrogen, phosphorus, and arsenic), and of salt formation by the addition of acids or of alkyl halides on the pyridyl nitrogen atoms; moreover all these atoms are in sufficiently close proximity to permit considerable mutual influence. Although the wartime conditions of this work did not allow us to investigate these properties under the rigidly comparable conditions that we should have desired, we have been able to study this question in some detail. For this purpose, we have first added an ethanolic solution of the compound to a considerable excess of saturated ethanolic hydrogen chloride, and the hydrochloride of the compound which separated has then been confined in a vacuum over powdered sodium hydroxide. The composition of the hydrochloride thus obtained is shown in the third column of Table I. It must be emphasized that these values indicate the maximum number of molecules of hydrochloric acid that can be *stably* united to the compounds; in certain cases higher poly-hydrochlorides may possibly have been initially formed and then reverted to the lower and more stable salts during isolation and drying. Further evidence of salt

formation was obtained by similarly adding ethanolic solutions of each of the nine compounds in turn to a considerable excess of ethanolic picric acid (fourth column, Table I). The picrates thus obtained have been purified by recrystallization: since however it was possible that a poly-picrate which was stable in the presence of free picric acid might lose picric acid on recrystallization, the identity of the "crude" and the recrystallized picrate was always checked by analyses or mixed melting point determinations. The comparative reaction with these two acids is of value, because it may indicate the partial suppression of the basic properties of an amino group; such a group might remain sufficiently basic for combination with a strong acid such as hydrochloric acid, but insufficiently so for combination with the much weaker picric acid.

We have then investigated quaternary salt formation under four different conditions (cf. columns 5-8, Table I). Most of our compounds have been (a) refluxed with a benzene solution of methyl iodide, (b) refluxed with pure methyl iodide, (c) heated with methyl iodide in nitromethane solution at *ca.* 50°, (d) heated with methyl iodide in methanol at 100° in a sealed tube; in all these experiments a considerable excess of methyl iodide was of course employed. Theoretical considerations indicate that (a)-(d) provide increasingly favorable conditions for maximum quaternary salt formation, and our experience has confirmed this indication. Menschutkin (26) has shown that the rate of quaternary salt formation is increased in solvents of high dielectric constant. Benzene has the low constant of 2.3, whereas nitromethane has the high value of 38.2 (27), and is known to promote vigorously quaternary salt formation with methyl iodide (25). Methanol has also a high constant of 32.5 (27); moreover the use of a sealed tube in the experiments with methanolic methyl iodide enabled a comparatively high temperature to be employed without serious risk of dissociation of the quaternary salt.

In the case of the phosphine and arsine derivatives, further information regarding the position of the acid or alkyl residues could be obtained by first converting the tertiary phosphine or arsine group to the 4-covalent state. For this purpose, each of the tertiary phosphines was also converted to the corresponding phosphine sulfide, and the latter then subjected to the above treatment with acids and with methyl iodide. The mono-2-pyridyldiphenylarsine and the tri-2-pyridyl-phosphine and -arsine were also converted to the corresponding oxides, and the behavior of the latter towards picric acid then investigated.

The results for the nine original compounds and for the sulfide and oxide derivatives are collected in Table I; for convenient reference, the melting points of the parent compounds are collected in the second column.

The interpretation of the results incorporated in Table I rests on the following three well-established facts.

(i) The additive properties (as shown in salt formation) of trivalent Group VB elements in an organic molecule may be profoundly influenced by the near presence of a positive charge in the molecule. This point has already been discussed.

(ii) The nitrogen atom in the pyridine molecule tends to withdraw electrons

from the 2 and the 4 positions, and pyridine consequently bears a chemical resemblance to nitrobenzene [Bradley and Robinson (28)]. This inductive effect away from the 2 and the 4 positions in pyridine is supported by many chemical properties which are too familiar to require citation. It is also to be expected on theoretical grounds. Since nitrogen is more electronegative than

TABLE I
REACTIONS OF AMINES, PHOSPHINES, ARSINES, AND DERIVATIVES
Py = 2-Pyridyl Ph = Phenyl

COMPOUND	M.P. °C	COMBINATION WITH ACIDS		COMBINATION WITH METHYL IODIDE			
				Moles Methyl iodide in			
		Moles HCl	Moles Picric Acid	(a) Boiling Benzene	(b) Boiling Methyl iodide	(c) Nitrometh- ane at ca. 50°	(d) Methanol at 100°
PyPh ₂ N	105		1		1		1
PyPh ₂ P	85		1		1	1	1
PyPh ₂ As	62		1	1	2		
Py ₂ PhN	94		1		1	1 + 2	2
Py ₂ PhP	96	2	2		1	1	(d)
Py ₂ PhAs	88	2	2		2		2
Py ₂ N	130	2	1		1	1 + 2	2
Py ₃ P	115	3	2	1		1 + (e)	(d)
Py ₃ As	85	3	2	2	2	2	3
PyPh ₂ PS	119		0		0	1	1 + (g)
PyPh ₂ AsO			1				
Py ₂ PhPS	141	2	1	0	0	1	(d)
Py ₃ PS	161		1		1	1	(d) + (f)
Py ₃ PO	209		1				(d)
Py ₃ AsO			1				

(d) 2,2'-Dipyridyl dimethiodide.

(e) Di-2-pyridylmonomethylphosphine dimethiodide monohydrate.

(f) Mono-2-pyridyldimethylphosphine sulfide monomethiodide.

(g) Trimethylsulfonium iodide.

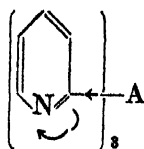
carbon, canonical forms of pyridine such as XXXIVa and XXXIVb will play a much more prominent part in the resonance hybrid than any analogous forms in the benzene hybrid [Pauling (29)].



XXXIVa



XXXIVb



XXXV

Consequently the 2-pyridyl radical will be more electronegative than the phenyl radical, and therefore the central nitrogen, phosphorus or arsenic atoms in, for example, the tri-2-pyridyl derivatives (XXXV, where A = N, P, or As) will be less reactive than those in the triphenyl analogs, because the inductive effect away from each central atom will place a greater restraint on its lone pair of electrons.

(iii) The third factor, originally suggested by Ingold (7, 30), is that the inductive effect is transmitted more readily through a nitrogen atom than through the larger phosphorus and arsenic atoms. The evidence for this statement can be briefly outlined. It is well known that the direct attachment of an atom bearing an integral positive charge to the benzene nucleus causes almost exclusively *meta*-substitution irrespective of the nature of the atom [Vorländer (31)]. If a CH₂ group is inserted between the atom and the benzene ring, the *meta*-substitution will still persist in the benzyl group, but will be less prominent because of the weaker inductive effect of the more distant positively charged atom. Ingold *et al.* (7, 8) have determined the amount of *meta*-nitration which phenyl-trimethyl-ammonium, -phosphonium, -arsonium and -stibonium picrates

TABLE II

AMOUNT OF *meta*-NITRATION IN PHENYLTRIMETHYL- AND BENZYLTRIMETHYL-AMMONIUM, -PHOSPHONIUM, -ARSONIUM, AND -STIBONIUM PICRATES

	N	P	As	Sb
PhMe ₃ derivative.....	100%	100%	98%	86%
BzMe ₃ ".....	88	10	3.4	—

undergo, and also that shown by the corresponding benzyltrimethyl derivatives. Their results are summarized in Table II.

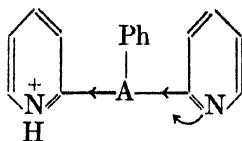
They suggest, in explanation of these results, that the charge on the above cations resides in the nucleus of the Group V B atom concerned, and that the influence of this charge will consequently be less the greater the number of outer electronic shells which this atom possesses. Hence the larger atoms could be regarded as exerting a damping action on the inductive effect initiated by the charge; therefore the amount of *meta*-substitution, dependent on this effect, falls steadily from nitrogen through to antimony.

Independent confirmation of this factor has been obtained by Davies and Lewis (32), who have studied the effect of a *para*-substituent X upon the rate of reaction of tertiary amines and phosphines, *p*-XC₆H₄AR₂ (A = N or P), with alkyl halides. Thus the introduction of a *para*-methyl group into the amine C₆H₅NR₂ increased its reactivity towards methyl iodide twice as much as that caused by the introduction of the same group into the corresponding phosphine C₆H₅PR₂; similarly the introduction of a *para*-chloro group into the above amine decreased its reactivity almost twice as much as that of the phosphine. Further, the introduction of *para*-substituents had less effect on the basic strengths of the above phosphines than on that of the amines (33). In all these examples it is

clear that the electronic influence of the *para*-substituent is being transmitted less readily through the phosphorus than through the nitrogen atom.

In interpreting the reactions summarized in Table I, the action of the acids on the parent compounds will be considered first, and then that of methyl iodide. From the above discussion it is clear that the "central" nitrogen, phosphorus, and arsenic atoms in the nine tertiary amines, phosphines, and arsines must be neutral, and that salt formation with acids therefore can occur only at the pyridyl nitrogen atoms. Each of the three mono-2-pyridyldiphenyl derivatives forms a monopicate, clearly by salt formation at the 2-pyridyl nitrogen atom. The mono-2-pyridyldiphenylphosphine sulfide does not form a picrate, however. This is not unexpected, because the positive charge on the phosphorus atom (due to the polar P^+-S^- link) will tend to deactivate the basic nitrogen atom. It is noteworthy that Davies and Mann (25) found that neither phenyl-*p*-bromophenyl-2-pyridylphosphine sulfide nor phenyl-*p*-bromophenyl-*p*-dimethylaminophenylphosphine sulfide would form salts with acids, the same deactivating mechanism being present. In the case of the mono-2-pyridyldiphenylarsine oxide, $PyPh_2AsO$, a new factor enters, and the arsine oxides will be discussed later.

In the di-2-pyridylmonophenyl series, it is significant that whereas the phosphine and arsine exerted their normal basicity and formed dipicrates, the amine formed only a monopicate. It is clear that directly one of the pyridyl groups forms a salt (XXXVI), the inductive effect initiated by this positive pole will



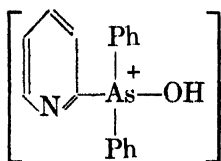
XXXVI

tend to deactivate the nitrogen atom of the second pyridyl group. When in the pyridylamine these two groups are separated only by the light central nitrogen atom (XXXVI, $A = N$), this inductive effect is not seriously impeded, and the nitrogen atom of the second pyridyl group is forced into inactivity. When, however, the two groups are separated by the larger phosphorus and arsenic atoms (XXXVI, $A = P$ or As), the inductive effect is so damped that the nitrogen atom of the second pyridyl group remains sufficiently basic for salt formation, and dihydrochlorides and dipicrates result. In the di-2-pyridylmonophenylphosphine sulfide, the positive charge on the phosphorus atom will however strengthen the inductive effect away from the second pyridyl nitrogen atom, which now becomes partly inactivated, and consequently the sulfide molecule, although forming a rather unstable dihydrochloride, now forms only a monopicate.

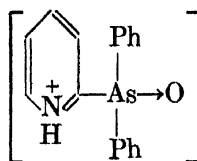
Precisely similar results are furnished by the tri-2-pyridyl compounds. In the presence of a strong acid such as hydrochloric acid, all three nitrogen atoms in the phosphine and arsine are sufficiently basic for salt formation, the central phosphorus and arsenic atoms again damping the inductive effect, but in the amine this effect is sufficiently strong to deactivate one of the pyridyl groups,

and only a dihydrochloride is formed. It is very interesting to note that this deactivating influence must be present in the phosphine and arsine also, although not sufficiently strongly to prevent trihydrochloride formation, because in these two compounds the third nitrogen atom cannot hold a molecule of the weaker picric acid, and the phosphine and arsine consequently form only dipicrates; in the pyridylamine the stronger inductive effect similarly deactivates a second pyridyl nitrogen atom towards picric acid (although not to the stronger hydrochloric acid), and this amine therefore forms only a monopicrate. The behavior of these three compounds with the two acids forms a striking confirmation of our theoretical suggestions. Again in the tri-2-pyridylphosphine sulfide, the basicity towards picric acid drops from two to one by the effect of the extra positive pole produced by combination with sulfur.

There is little doubt concerning the structure of the picrates given by the tertiary arsine oxides. It is well known that triarylarisines will not combine with picric acid, but that their oxides readily give crystalline picrates, and will combine even with such weak acids as *p*-toluenesulfonamide to give crystalline salts (34); these derivatives must therefore have the structure $[R_3AsOH]OC_6H_2(NO_2)_3$ and $[R_3AsOH] \cdot NHSO_2C_6H_5$ respectively (R = aryl group). It is therefore reasonably certain that the picrate formed by mono-2-pyridyldiphenylarsine oxide has the cation XXXVII. The possibility that the cation has the isomeric structure XXXVIII is discounted by the above argument and also by the following consideration.



XXXVII



XXXVIII

If the picrate had the cation XXXVIII, it would follow that the arsenic-oxygen link did not affect the pyridyl group, since the proton had united with the pyridyl nitrogen atom precisely as in the parent mono-2-pyridyldiphenylarsine itself. There should by analogy therefore be no difference between the behavior of tri-2-pyridylarsine and its oxide towards picric acid; yet the tertiary arsine unites with two molecules and the arsine oxide with only one molecule of picric acid. It follows that the cation of both arsine oxides is of type XXXVII, and that the positive charge on the arsenic atom is sufficiently strong to deactivate the pyridyl nitrogen atoms. A similar argument applies to the tri-2-pyridylphosphine oxide.

The interpretation of the results of quaternary salt formation with methyl iodide is clearly more complex, because an extra factor now enters, since theoretically the "central" nitrogen, phosphorus, or arsenic atom can also now unite with the methyl iodide. It is most convenient to discuss first the three amines, then the corresponding phosphines and arsines in turn.

It will be seen that mono-2-pyridyldiphenylamine combined with only one molecule of methyl iodide. Since the central nitrogen atom in this amine is less

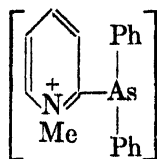
reactive than that in triphenylamine, and the latter does not combine with methyl iodide, it is certain that our monomethiodide has the quaternary group on the 2-pyridyl nitrogen atom. Furthermore, it is significant that di-2-pyridylmonophenylamine and tri-2-pyridylamine under like conditions behave precisely similarly with methyl iodide, and that a dimethiodide is the highest quaternary salt formed. It follows that one of the pyridyl nitrogen atoms in tri-2-pyridylamine must have been inactivated by the quaternary salt formation, and that the methyl iodide molecules have undoubtedly added on to the other two pyridyl nitrogen atoms; the positive pole on either of these atoms is insufficient to deactivate the other atom towards methyl iodide, but their combined effect does deactivate the third group. It is almost certain therefore that in the di-2-pyridylmonophenyl derivative, the methyl iodide units are also on the pyridyl nitrogen atoms. Incidentally, the behavior of both these tertiary amines towards methyl iodide illustrates vividly the increasing potency of the four sets of conditions (a)-(d) for methiodide formation that we have employed.

With regard to the three tertiary phosphines, it is highly significant that all three combined with only one molecule of methyl iodide. Now there is both qualitative and quantitative evidence [Davies and Lewis (32)] that under comparable conditions the rate of reaction of a tertiary phosphine with an alkyl iodide is greater than that of the corresponding arsine, which in turn is greater than that of the corresponding amine. Our results indicate strongly therefore that all our phosphines have combined with methyl iodide to give phosphonium salts, and the strong positive charge on the phosphonium atom has effectively deactivated all the pyridyl nitrogen atoms. The constitution of these methiodides is further confirmed by the following considerations. If the methyl iodide molecule, instead of combining with the phosphorus atom, had combined with the nitrogen atom of one of the pyridyl groups, the positive pole thus produced would have exerted a weaker deactivating effect on a neighboring pyridyl nitrogen atom than it would in the corresponding amine, because this effect would have to pass through the central phosphorus atom instead of the lighter nitrogen atom. Consequently our di- and tri-pyridylphosphines should have combined with more molecules of methyl iodide than the corresponding amines. Actually the reverse was the case: *e.g.*, di-2-pyridylmonophenylphosphine gave only a monomethiodide in nitromethane, whereas di-2-pyridylmonophenylamine gave both a mono- and a di-methiodide under these conditions. There is no doubt therefore that all our phosphine methiodides are quaternary phosphonium salts.

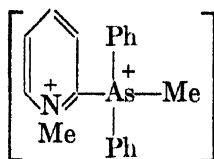
In the three tertiary phosphine sulfides, however, this phosphonium salt formation has been impossible; the positive charge on the phosphorus atom in the sulfides is however much weaker than that in the phosphonium salts, and the deactivating effect is therefore less intense; consequently in each of the sulfides one of the pyridyl nitrogen atoms has been able to combine with methyl iodide, although the conditions of combination were throughout more vigorous than those required for methyl iodide addition to the tertiary phosphines themselves.

Considering our tertiary arsines, it is noteworthy that mono-2-pyridyldiphenylarsine gave a monomethiodide with methyl iodide in benzene, but a di-

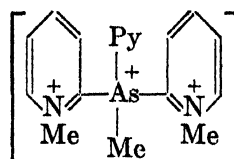
methiodide with methyl iodide alone. Now pyridine reacts much more vigorously with methyl iodide than triphenylarsine does, and it would be expected therefore that methyl iodide would attack the pyridyl nitrogen first, and then attack the tertiary arsenic atom only under more vigorous conditions. Consequently our monomethiodide should have the cation XXXIX and the dimethiodide the cation XL.



XXXIX



XL



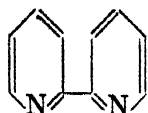
XLI

The suggestion that methyl iodide addition here occurs preferentially on the pyridyl nitrogen atoms receives strong support from the results obtained with the other arsines. It will be noticed that under the most vigorous conditions (methyl iodide in methanol at 100°), di-2-pyridylmonophenylarsine gave a dimethiodide and tri-2-pyridylarsine a trimethiodide. Now if the latter had been an arsonium salt, *i.e.* had it possessed the cation XLI, there is no reason why di-2-pyridylmonophenylarsine should not also have formed a similar trimethiodide. It follows that in both this dimethiodide and the trimethiodide, the addition of methyl iodide has occurred solely at the pyridyl nitrogen atoms, and that the tertiary arsenic atom has remained unchanged. This indicates that in the quaternary salts of the arsines a positive charge on at least two pyridyl nitrogen atoms is required to deactivate the arsenic atom under the conditions we have employed.

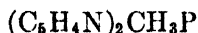
It will be seen therefore that our theory of deactivation by inductive effects initiated by neighboring positive poles both interprets and correlates the results summarized in Table I, which might otherwise seem largely disconnected in their apparent variety and differences.

One further point deserves mention, although strictly it lies beyond the scope of the above investigation. It will be noticed that certain tertiary phosphines and phosphine sulfides when exposed to the most vigorous methyl iodide attack underwent decomposition, with splitting off of the pyridyl groups. These decompositions usually gave a mixture of products which were difficult to separate; in no case do we claim to have isolated every component of the mixture, but the nature of the pure components that we have isolated leaves little doubt that the process consists essentially of a progressive replacement of 2-pyridyl groups by methyl groups. Thus both di-2-pyridylmonophenylphosphine and tri-2-pyridylphosphine under the most vigorous conditions of methyl iodide attack gave the dimethiodide of 2,2'-dipyridyl (XLII), but the latter phosphine also gave the dimethiodide of di-2-pyridylmonomethylphosphine (XLIII). When tri-2-pyridylphosphine sulfide was similarly treated, the process went one stage further, with the formation of the monomethiodide of mono-2-pyridyldimethylphosphine sulfide (XLIV) in addition to the dimethiodide of 2,2'-dipyridyl. It is clear

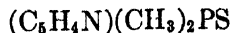
therefore that the 2-pyridyl groups must initially break off as free radicals, which then unite in pairs.



XLII



XLIII



XLIV



XLV

The ultimate fate of the sulfides is strongly indicated by the fact that mono-2-pyridyldiphenylphosphine sulfide, similarly treated, gave trimethylsulfonium iodide (XLV). We have no evidence that phenyl groups are evicted in this way, and it is probable that the 2-pyridylphenylphosphines would ultimately give the corresponding phenylmethylphosphonium iodides, whilst tri-2-pyridylphosphine would give tetramethylphosphonium iodide, and that the phosphine sulfides behave similarly, with the sulfur atom splitting off as trimethylsulfonium iodide. No similar degradation of the corresponding amines and arsines with methyl iodide has been detected. It is noteworthy however that when tri-2-pyridylamine was treated with tin and hydrochloric acid in an attempt to prepare tri-2-piperidylamine, the only product isolated was di-2-pyridylamine, $(\text{C}_6\text{H}_4\text{N})_2\text{NH}$, one of the pyridyl groups having thus been shed in this reaction also.

EXPERIMENTAL

2-Aminopyridine was prepared by the method of Tschitschibabin and Seide (21). 2-Bromopyridine, prepared by the method of Craig (37) in 85% yield, had b.p. $72-74^\circ/10.5$ mm., $79.5-82.5^\circ/16$ mm., and $90-92^\circ/24$ mm. Diphenylmonochlorophosphine was prepared by the action of diphenylmercury on phenyldichlorophosphine (38) and obtained as a colorless liquid, b.p. $193-194^\circ/26$ mm.

The letter (a), (b), (c), or (d) is given before each experiment with methyl iodide, in accordance with the conditions employed as cited in column 5, 6, 7, or 8 respectively in Table I.

Mono-2-pyridyldiphenylamine. A mixture of diphenylamine (16.9 g.), 2-bromopyridine (9.5 cc., 1 mole), anhydrous potassium carbonate (10 g.), copper bronze (0.25 g.), potassium iodide (ca. 0.2 g.), and amyl alcohol (5 cc.) was gently refluxed for 9 hours, and then steam-distilled to remove amyl alcohol and unchanged 2-bromopyridine. The cold residue was extracted with chloroform, and the chloroform layer then shaken thrice with dilute hydrochloric acid to extract the required amine, leaving unchanged diphenylamine in the chloroform. The united acid extracts were basified with sodium hydroxide, and the precipitated amine extracted with benzene. After drying, the benzene was distilled and the solid residue recrystallized from aqueous ethanol (charcoal). The amine had m.p. 105° ; yield, 1.9 g. (7.7%). Tschitschibabin (21) gives m.p. 104° .

Monopicate. A hot solution of the amine (0.3 g.) and picric acid (1.5 g., 5.3 moles) in ethanol (30 cc.) on cooling gave yellow crystals of the monopicate, m.p. 174° , unchanged by recrystallization from ethanol.

Anal. Calc'd for $\text{C}_{17}\text{H}_{14}\text{N}_2 \cdot \text{C}_6\text{H}_3\text{N}_3\text{O}_7$: C, 58.1; H, 3.6.

Found: C, 58.4; H, 3.9.

Action of methyl iodide. (b). A solution of the amine (0.3 g.) in methyl iodide (5 cc., 66 moles) was refluxed for 4 hours, a yellow crystalline deposit separating very rapidly however. The excess of methyl iodide was evaporated, and the residue when recrystallized from ethanol gave the *monomethiodide*, m.p. 192° .

Anal. Calc'd $C_{18}H_{17}IN_2$: C, 55.7; H, 4.4.

Found: C, 56.2; H, 4.3.

(d) A solution of the amine (0.5 g.) in methanol (0.25 cc.) containing methyl iodide (0.4 cc., 3.2 moles) was heated in a sealed tube at 100° for 8 hours. The cold, clear, brown solution was poured into ether, and the precipitated crystals, when recrystallized from ethanol, had m.p. 192° alone and when mixed with the above monomethiodide.

Mono-2-pyridyldiphenylphosphine. The magnesium-2-pyridyl bromide required for this and for subsequent phosphine and arsine syntheses was prepared essentially by the method of Overhoff and Proost (39) as modified by Davies and Mann (25). One description in detail suffices for all. A round-bottomed flask of 1-liter capacity was fitted with a reflux water-condenser, stirrer, dropping-funnel, and an inlet-tube through which a current of nitrogen could be passed throughout the experiment; the necks of this condenser and dropping-funnel were closed with calcium chloride tubes. Magnesium turnings (15 g.) were placed in the flask, and a solution of ethyl bromide (1 cc., 0.02 mole) in ether (50 cc.) added. A crystal of iodine was also added to initiate the reaction. When the ether was boiling, the stirrer was started, and a solution of pure, dry 2-bromopyridine (28.8 cc., 0.49 mole) and ethyl bromide (10.5 cc., 0.23 mole) in ether (250 cc.) was run in at such a rate that gentle boiling continued. The addition required 75 minutes, and the formation of the Grignard reagent was then completed by refluxing the mixture for a further 2 hours. The mixture was then immersed in cold water ($18-22^\circ$), and the stirring continued whilst a solution of diphenylmonochlorophosphine (43.2 g., 0.32 mole) in ether (275 cc.) was added over a period of 2 hours. The product was then refluxed for 2 hours, cooled in ice, and hydrolyzed by the cautious addition of a solution of ammonium chloride (140 g.) in cold water (275 cc.). The stirring and the passage of nitrogen were now stopped, the mixture filtered, and the ethereal layer separated, dried (sodium sulfate), and the solvent evaporated. The residue when fractionally distilled gave the fractions: (a) b.p. $37-114^\circ/0.05$ mm.; (b) b.p. $132-155^\circ/0.05$ mm.; (c) b.p. $160-180^\circ/0.05$ mm. Fraction (b) crystallized on scratching, and when recrystallized from aqueous methanol gave the pure mono-2-pyridyldiphenylphosphine, colorless crystals, m.p. $84-85^\circ$; yield 8.2 g. (16%). Fraction (c) was converted into the picrate described below, and the latter recrystallized: treatment with alkali gave a further crop of the phosphine, weighing 2.3 g. (4.4%), m.p. 85° . Fraction (a), which probably contained 2,2'-dipyridyl and other products, did not crystallize. It should be noted that in the first preparation fraction (b) refused to crystallize: the crude phosphine had to be converted to the picrate, purified as such, and then regenerated by the action of alkali (see corresponding arsine); this treatment gave the crystalline phosphine in 98% yield, and fraction (b) obtained in subsequent preparations then crystallized readily.

Anal. Calc'd for $C_{17}H_{14}NP$: C, 77.5; H, 5.3; N, 5.3

Found: C, 77.0; H, 5.5; N, 5.55.

Monopicrate. The addition of the phosphine (0.15 g.) to picric acid (0.4 g., 3 moles) each dissolved in ethanol, precipitated the phosphine monopicrate, m.p. $132-133.5^\circ$, increased to $137-138^\circ$ by recrystallization from ethanol containing some acetone.

Anal. Calc'd for $C_{17}H_{14}NP \cdot C_6H_3N_3O_7$: C, 56.1; H, 3.5; N, 11.4.

Found: C, 55.5; H, 3.3; N, 11.5.

Action of methyl iodide. (b) A mixture of the phosphine (0.3 g.) and cold methyl iodide (5 cc., 70 moles) gave a clear solution, which however rapidly became cloudy and an oily layer collected on the surface. The mixture was refluxed for 30 minutes, during which the oil soon crystallized. The methyl iodide was then evaporated, and the residue purified by dissolving in ethanol, filtering, and adding much ether. The monomethiodide separated as colorless crystals, m.p. $141-142^\circ$.

Anal. Calc'd for $C_{18}H_{17}INP$: C, 53.5; H, 4.2.

Found: C, 52.55; H, 4.2.

This methiodide was converted in the usual way to the *monomethopicate*, yellow crystals from ethanol, m.p. 98–99°.

Anal. Calc'd for $C_{24}H_{19}N_4O_7P$: C, 56.9; H, 3.9.

Found: C, 56.9; H, 4.0.

(c) A mixture of the phosphine (0.5 g.), nitromethane (3.5 cc.), and methyl iodide (2.0 cc., 17 moles) was heated at 47–50° for 48 hours. The solution remained clear on cooling, but the addition of ether precipitated a red oil, which crystallized on scratching. The crystals (0.7 g.), after purification as above, had m.p. 141–142°, unchanged by admixture, with the previous product.

(d) A mixture of the phosphine (0.5 g.), methanol (0.3 cc.), and methyl iodide (0.5 cc., 4.3 moles) was heated in a sealed tube at 100° for 8 hours. The cold product, consisting of a heavy red oil covered by a pale yellow liquid, would not crystallize. It was therefore extracted with cold ether, and the insoluble oil then dissolved in cold water: the aqueous solution, when treated with sodium picrate, precipitated the above monomethopicate, m.p. 98–99° after crystallization from ethanol, unchanged by admixture with the above specimen.

Mono-2-pyridyldiphenylphosphine monosulfide. A solution of the phosphine (0.507 g.) and of sulfur (0.062 g., 1 atom) in benzene (10 cc.) was refluxed for 2 hours. The benzene was then evaporated and the residue, when recrystallized from ethanol, gave colorless crystals of the sulfide, m.p. 119°.

Anal. Calc'd for $C_{17}H_{14}NPS$: C, 69.1; H, 4.8.

Found: C, 69.1; H, 4.95.

This sulfide, which was only slightly soluble in cold ethanol, dissolved readily in saturated ethanolic hydrogen chloride, but the solution in the latter solvent when evaporated in a desiccator at room temperature gave a sticky, glassy residue which, when crystallized from ethanol, deposited the pure sulfide. It is probable, therefore, that the sulfide forms a hydrochloride in the acid solution, but the salt is too unstable for isolation.

A saturated ethanolic solution of the sulfide gave no precipitate when mixed with a similar solution of picric acid, whereas a saturated benzene solution of the acid merely dissolved the unchanged sulfide.

Action of methyl iodide. (b) A solution of the sulfide (0.15 g.) in methyl iodide (3 cc., 100 moles) was refluxed for 5 hours. Evaporation gave a residue of the unchanged sulfide, m.p. 118–119° after recrystallization from ethanol, unchanged by admixture with the original specimen.

(c) A solution of the sulfide (0.3 g.) in nitromethane (2.5 cc.) containing methyl iodide (1.5 cc., 24 moles) was maintained at 47–54° for 60 hours, and then cooled and poured into much ether. The solvent was then decanted from the sticky brown precipitate, which readily crystallized when rubbed with ethanol: recrystallization from ethanol then gave the *monomethiodide*, pale yellow crystals, m.p. 167.5–168.5° (effer.).

Anal. Calc'd for $C_{18}H_{17}INPS$: C, 49.4; H, 3.9.

Found: C, 48.9; H, 3.7.

(d) A mixture of the sulfide (0.35 g.), methanol (0.25 cc.), and methyl iodide (0.4 cc., 5.3 moles) was heated in a sealed tube at 100° for 7.5 hours. The cold product, which consisted of a deep red liquid containing some brown semi-solid material, was stirred with a small quantity of methanol, giving a solution containing some colorless crystals. The latter were filtered off, and the filtrate poured into much ether, whereby yellow crystals of the above monomethiodide were precipitated, m.p. 167.5–168.5° (effer.) (alone and mixed) after recrystallization from ethanol.

The colorless crystals were highly soluble in water, and were recrystallized from methanol; when heated in a capillary tube, the material dissociated and disappeared at

ca. 200°, depending on the rate of heating. The aqueous solution gave ionic iodine, and analysis showed that the compound was trimethylsulfonium iodide, although a low sulfur analysis was obtained.

Anal. Calc'd for C_4H_9IS : C, 17.6; H, 4.45; S, 15.7.
Found: C, 17.4; H, 4.7; S, 13.1.

It has previously been stated that when triphenylphosphine sulfide (35) and phenyl-*p*-bromophenyl-2-pyridylphosphine sulfide (25) are heated in a sealed tube with an excess of methyl iodide at 100°, tetramethylphosphonium iodide is formed, the latter having been identified by its properties and its iodine content. We have confirmed the iodine analysis quoted for these samples, but find that in spite of their excellent crystalline form they are actually impure samples of trimethylsulfonium iodide and hence have been incorrectly identified. To confirm this, we have heated triphenylphosphine sulfide (7.3 g.) with methyl iodide (15.5 cc., 10 moles) in a sealed tube at 100° for 4 hours. The crude product yielded unchanged triphenylphosphine sulfide, m.p. 159–160°, triphenylmethylphosphonium iodide, m.p. 166.5–167.5° (initially present largely as a polyiodide), and trimethylsulfonium iodide.

The latter was recrystallized thrice from ethanol, and then dissociated at 201–203°, with preliminary softening.

Anal. Found: C, 17.3; H, 4.35.

Mono-2-pyridyldiphenylarsine. This was prepared precisely as the corresponding phosphine, the Grignard reagent being prepared from magnesium (5 g.), which was treated first with ethyl bromide (0.5 cc.) in ether (20 cc.) to initiate the reaction, and then with a mixture of 2-bromopyridine (9.6 cc., 0.49 mole) and ethyl bromide (3.5 cc., 0.23 mole) in ether (100 cc.). This reagent was treated with a solution of diphenylmonochloroarsine (11.5 g., 0.21 mole) in ether (100 cc.), then refluxed for 2 hours, and finally hydrolyzed at 0° by ammonium chloride (50 g.) dissolved in water (200 cc.). The crude product when distilled at 0.2 mm. pressure gave the fractions: (a) b.p. 94–160°; the first portion crystallized and was undoubtedly 2,2'-dipyridyl; (b) b.p. 160–192°, a liquid distillate; (c) b.p. 192–250°, a viscous syrup. Fraction (c) could not be induced to crystallize. It was therefore treated with an excess of ethanolic picric acid solution, which precipitated yellow crystals (3.7 g.) of the *monopicrate* of the arsine; this picrate, when recrystallized from ethanol containing a small amount of acetone, had m.p. 171.5–172.5°.

Anal. Calc'd for $C_{17}H_{14}AsN \cdot C_6H_3N_3O_7$: C, 51.5; H, 3.2.
Found: C, 52.0; H, 3.7.

This picrate was decomposed by shaking with a mixture of aqueous sodium hydroxide and ether until no solid remained; the ethereal solution was then separated, and repeatedly shaken with aqueous sodium hydroxide until colorless. It was then washed with water, dried (sodium sulfate), filtered, and evaporated. The residue, when recrystallized from aqueous ethanol (charcoal), gave colorless crystals of the arsine m.p. 62°.

Anal. Calc'd for $C_{17}H_{14}AsN$: N, 4.6. Found: N, 4.6.

In subsequent preparations, fraction (c) crystallized when seeded with the pure arsine. Solidification however was never complete, and purification was always effected through the picrate as before; evaporation of the ethereal solution gave the pure arsine without further crystallization. Yield of pure arsine, 9.4%.

Action of methyl iodide. (a) Methyl iodide (1.5 cc., 22 moles) was added to a solution of the arsine (0.34 g.) in benzene (10 cc.), and the mixture refluxed for 4 hours. The brown oil which separated did not crystallize on cooling. The solvent was therefore decanted, and the residual syrup stirred with ether; the latter was decanted and the residue stirred with a very small quantity of acetone. Yellow crystals of the *monomethiodide* remained, and were purified by precipitation from an ethanolic solution with ether; m.p. 160–162°.

Anal. Calc'd for $C_{18}H_{17}AsIN$: C, 48.1; H, 3.8.

Found: C, 47.85; H, 4.0.

The benzene which had been decanted was evaporated, and the residue readily crystallized; when purified by the above ethereal precipitation it furnished a second crop of the monomethiodide, m.p. 158–161° (alone and mixed) which was further identified as the monomethopicrate, m.p. 119°. It would appear therefore that this monomethiodide is the only product in this experiment.

(b) A solution of the arsine (0.5 g.) in methyl iodide (10 cc., 100 moles) was refluxed for 3.25 hours and then evaporated. The crystalline dark brown residue was too deliquescent for recrystallization. It was therefore mixed with an excess of sodium picrate, both in ethanolic solution: the yellow crystalline precipitate (m.p. 150.5–152°, increased to 152.5–153° by recrystallization from ethanol) was dried in a vacuum over phosphoric anhydride for several days and thus gave the *dimethopicrate monohydrate*.

Anal. Calc'd for $C_{21}H_{24}AsN_7O_{14} \cdot H_2O$: C, 45.8; H, 3.2; N, 12.1.

Found: C, 45.8; H, 2.5; N, 12.2.

Mono-2-pyridyldiphenylarsine dibromide and oxide. Bromine (0.075 cc., 1 mole) was added dropwise to a solution of the arsine (0.46 g.) in acetic acid (10 cc.) which was stirred meanwhile and cooled in water. The solution deposited colorless crystals of the arsine dibromide, which were washed with acetic acid and rapidly transferred to a vacuum desiccator. It was exceedingly deliquescent.

Anal. Calc'd for $C_{17}H_{14}AsBr_2N$: Br, 34.2. Found: Br, 35.0.

The acetic acid mother liquor was poured into an excess of 30% aqueous sodium hydroxide and refluxed for 1 hour. The oil which had separated was extracted with chloroform, and the latter then washed with water, dried, and evaporated. The residual oil would not crystallize: it was therefore added to ethanolic picric acid solution. The yellow *arsine oxide monopicrate* thus obtained had m.p. 138–141.5°, increased to 144–145° by recrystallization from ethanol.

Anal. Calc'd for $C_{17}H_{14}AsNO \cdot C_6H_3N_3O_7$: C, 50.0; H, 3.1.

Found: C, 49.6; H, 3.4.

When hydrogen sulfide was passed through an ethanolic solution of the crystalline dibromide, a small amount of sulfur was deposited. The filtered solution was evaporated in a desiccator, but the residual oil did not crystallize. When treated with sodium carbonate solution, however, carbon dioxide was evolved, and the colorless solid arsine was deposited, m.p. 62° (alone and mixed) after crystallization from ethanol. The oil was therefore probably the hydrobromide of the arsine.

Di-2-pyridylmophenylamine. This was prepared essentially by the method of Wibaut and Tilman (23). The crude product was recrystallized first from light petroleum (b.p. 60–80°) and then from aqueous ethanol; m.p. 94°, yield of pure material, 15%. Wibaut and Tilman give m.p. 93°.

Picrate. The amine (0.3 g.) was added to a hot solution of picric acid (1.5 g., 5.4 moles) in ethanol (30 cc.). On cooling, the monopicrate separated as yellow crystals, m.p. 149–150°, unchanged by recrystallization from ethanol: a mixture of the "crude" and the recrystallized picrate also had m.p. 149–150°.

Anal. Calc'd for $C_{18}H_{13}N_3 \cdot C_6H_3N_3O_7$: C, 55.4; H, 3.4.

Found: C, 55.3; H, 3.6.

Action of methyl iodide. (b) The amine (0.3 g.) dissolved immediately in methyl iodide (5 cc., 66 moles) and a crystalline precipitate readily formed on warming; the mixture was however refluxed for 5 hours, and the methyl iodide then allowed to evaporate. The

residue, when twice recrystallized from ethanol, in which it was very soluble, gave the pure *monomethiodide*, which melted with effervescence over a range of 4–5° at *ca.* 193°, dependent on the rate of heating.

Anal. Calc'd for $C_{17}H_{18}IN_3$: C, 52.4; H, 4.15.

Found: C, 53.2; H, 3.95.

In view of the indefinite m.p., the iodide was added to aqueous sodium picrate solution, and the precipitated material when recrystallized from ethanol gave the yellow crystalline *monomethopicate*, m.p. 131–132°.

Anal. Calc'd for $C_{22}H_{18}N_6O_7$: C, 56.3; H, 3.7.

Found: C, 56.1; H, 3.6.

(c) A solution of the amine (0.5 g.) in nitromethane (4 cc.) containing methyl iodide (2.5 cc., 20 moles) was maintained at 48–53° for 48 hours, although crystals separated after the first few hours. The cold mixture was filtered, and the crystals, which were only slightly soluble in hot pure ethanol, were recrystallized from aqueous ethanol. The crystalline *dimethiodide* thus obtained melted sharply at *ca.* 189° with vigorous effervescence, the m.p. depending on the rate of heating.

Anal. Calc'd for $C_{18}H_{19}I_2N_3$: C, 40.7; H, 3.6.

Found: C, 40.8; H, 3.8.

Addition of dry ether to the nitromethane mother liquor precipitated a crop of monomethiodide, which after crystallization from ethanol had m.p. 189–199° (effer.), and which gave the monomethopicate, m.p. 131–132°, both alone and when mixed with the former specimen.

(d) A mixture of the amine (0.5 g.), methyl iodide (0.6 cc., 5 moles) and methanol (0.35 cc.) was heated in a sealed tube at 100° for 8 hours. The yellow crystalline product, when recrystallized from aqueous ethanol, gave the dimethiodide, m.p. 193° (effer.).

Anal. Found: C, 40.95; H, 3.7.

Di-2-pyridylmonophenylphosphine. This was prepared similarly to the diphenyl analog, a Grignard reagent prepared from magnesium (15 g.), ethyl bromide (11.5 cc., 0.25 mole), and 2-bromopyridine (28.8 cc., 0.49 mole) in ether (250 cc.) being treated with a solution of phenyldichlorophosphine (14 g., 0.13 mole) in ether (100 cc.). After the usual treatment and working-up, the residue from the evaporation of the solvent was distilled at 0.4 mm. pressure and gave the fractions. (i) b.p. 64–66°, a small quantity of a colorless liquid; (ii) b.p. 94–105°, which rapidly solidified and was undoubtedly 2,2'-dipyridyl; (iii) b.p. 160–196°, a pale yellow oil; (iv) b.p. 196–210°, a viscous red liquid which crystallized spontaneously. Fraction (iv) could be crystallized from methanol, ethanol, cyclohexane, or light petroleum (b.p. 60–80°); it was best crystallized from a mixture of ethanol and light petroleum (b.p. 40–60°) and afforded the pure phosphine, colorless crystals, m.p. 96°.

Anal. Calc'd for $C_{16}H_{13}N_2P$: C, 72.7; H, 5.0; N, 10.6.

Found: C, 72.3; H, 5.1; N, 11.1.

Dihydrochloride. An ethanolic solution of the phosphine (0.2 g.) was slowly added to a saturated ethanolic hydrogen chloride solution (30 cc.) with stirring and ice-cooling. No crystals separated, so the solution was evaporated in a vacuum desiccator over flaked sodium hydroxide. The pale yellow residual oil was finally obtained crystalline by repeated extractions with cold acetone, although the crystalline residue at this stage was extremely deliquescent. It was further purified by adding ether to its ethanol solution, whereby a sticky precipitate was formed which crystallized on scratching and was no longer deliquescent. These crystals of the dihydrochloride when heated in a capillary tube sintered at *ca.* 100° and melted at 185–187°; when the tube was plunged into a bath pre-

heated to 130°, the crystals melted with effervescence, resolidified and melted again at 185–187°.

Anal. Calc'd for $C_{16}H_{13}N_3P \cdot 2HCl$: Cl, 21.05. Found: Cl, 21.5.

Dipicrate dihydrate. Prepared in the usual way from warm solution, the crude dipicrate dihydrate separated initially as yellow crystals, m.p. 128–130°, increased to 130–131° by one recrystallization from ethanol.

Anal. Calc'd for $C_{16}H_{13}N_3P \cdot 2C_6H_3N_3O_7 \cdot 2H_2O$: C, 44.3; H, 3.05.

Found: C, 44.1; H, 2.8.

Action of methyl iodide. (b) When the phosphine (0.3 g.) was added to methyl iodide (5 cc., 70 moles), the clear solution initially obtained soon became turbid, and a brown oil floated on the surface. The mixture was refluxed for 1 hour, and the methyl iodide then evaporated. The crystalline residue was dissolved in ethanol, and the latter then treated with much ether; the precipitated oil when scratched solidified to very deliquescent crystals. When these were dissolved in acetone, however, and ether again added, colorless non-deliquescent crystals of m.p. 133–134° were deposited. These were further purified by solution in ethanolic acetone and reprecipitation with ether. The pure *monomethiodide* was thus obtained, colorless crystals, m.p. 134–135°.

Anal. Calc'd for $C_{17}H_{16}IN_3P$: C, 50.2; H, 4.0.

Found: C, 50.35; H, 4.3.

(c) A solution of the phosphine (0.5 g.) in nitromethane (4.5 cc.) containing methyl iodide (2.5 cc., 21 moles) was kept at 48–52° for 8 hours. The product furnished only the above monomethiodide, m.p. 133–134°, alone and mixed.

(d) A clear yellow solution of the phosphine (0.5 g.) in methanol (0.5 cc.) containing methyl iodide (0.7 cc., 5.9 moles) was heated in a sealed tube at 100° for 9 hours. The cold solid red product was thoroughly mixed with methanol, and the yellow crystals which remained were then recrystallized from aqueous ethanol. They then had m.p. 247° (dec.) and when treated with aqueous sodium picrate gave a methopicrate, which after recrystallization from ethanolic acetone had m.p. 162–163°, unchanged by admixture with an authentic specimen of 2,2'-dipyridyl dimethopicrate.

Di-2-pyridylmonophenylphosphine sulfide. This was prepared by the union of the phosphine (0.694 g.) and sulfur (0.084 g., 1 atom) in boiling benzene, and when recrystallized from ethanol gave colorless crystals, m.p. 141°.

Anal. Calc'd for $C_{16}H_{13}N_3PS$: C, 64.8; H, 4.4.

Found: C, 64.5; H, 4.2.

Dihydrochloride. A solution of the sulfide (0.3 g.) in warm ethanol (5 cc.) was added to a cold saturated ethanolic solution of hydrogen chloride (35 cc.). The clear solution when partly evaporated in a vacuum desiccator deposited white crystals of the dihydrochloride, m.p. 165–171° (eff.).

Anal. Calc'd for $C_{16}H_{13}N_3PS \cdot 2HCl$: C, 52.0; H, 4.1; N, 7.6.

Found: C, 51.9; H, 4.0; N, 7.6.

Subsequent analysis indicated that this dihydrochloride, on prolonged confinement over sodium hydroxide in a vacuum desiccator, underwent slow dissociation to the monohydrochloride.

Monopicrate. When a solution of the sulfide (0.15 g.) and of picric acid (0.6 g., 5 moles) in ethanol (10 cc.) was allowed to cool, hard yellow crystals of the monopicrate, m.p. 141.5–142.5°, separated. Recrystallization from ethanol left the m.p. unaffected, and a mixed m.p. determination showed that no change had occurred.

Anal. Calc'd for $C_{16}H_{13}N_3PS \cdot C_6H_3N_3O_7$: C, 50.25; H, 3.1.

Found: C, 50.55; H, 3.6.

Action of methyl iodide. (a) A solution of the sulfide (0.2 g.) in benzene (5 cc.) containing methyl iodide (1 cc., 24 moles) was gently refluxed for 4 hours, during which a red coloration developed. The solvent was evaporated, and the residue, when recrystallized from aqueous ethanol, gave the unchanged sulfide, m.p. 139–140°, alone and mixed.

(b) A mixture of the sulfide (0.2 g.) and methyl iodide (4 cc., 95 moles) was refluxed for 3 hours. The clear hot solution was evaporated, but the residue on recrystallization furnished only the unchanged sulfide, m.p. 140–141°, alone and mixed.

(c) A solution of the sulfide (0.3 g.) in nitromethane (2.5 cc.) and methyl iodide (1.5 cc., 24 moles) was maintained at 49–54° for 50 hours. The clear brown solution was cooled and treated with ether; the precipitated brown gum could not be obtained crystalline, and was therefore converted to the methopicate. Accordingly, the gum was extracted with boiling water, and the filtered chilled extract added to an excess of aqueous sodium picrate solution. The crude precipitated *monomethopicate monohydrate* had m.p. 189–196°, and when recrystallized from ethanolic acetone had m.p. 200–202° (dec.) with sintering at 190°.

Anal. Calc'd for $C_{22}H_{18}N_4O_7PS \cdot H_2O$: C, 49.5; H, 3.6.

Found: C, 49.7; H, 3.7.

(d) A mixture of the sulfide (0.2 g.), methanol (0.2 cc.), and methyl iodide (0.3 cc., 7 moles) was heated in a sealed tube at 100° for 9 hours. The yellow crystalline product, when washed with methanol and recrystallized from aqueous ethanol, gave 2,2'-dipyridyl dimethiodide, melting with decomposition above 244°.

Anal. Calc'd for $C_{12}H_{14}I_2N_2$: I, 57.7. Found: I, 57.7.

This specimen was converted into the dimethopicate, which after recrystallization from ethanolic acetone, had m.p. 161–162°, unchanged by admixture with an authentic sample.

Di-2-pyridylmonophenylarsine. To a Grignard reagent prepared from magnesium (15 g.) precisely as in the preparation of the phosphine analog, a solution of phenyldichloroarsine (17.5 g., 0.13 mole) in ether (100 cc.) was added over a period of 1.5 hours. After the usual refluxing and subsequent working up, the residue on distillation gave the fractions: (i) b.p. 80–196°/0.1 mm.; (ii) 196–230°/0.2 mm. The latter crystallized spontaneously; it was freely soluble in ether, benzene, methanol, and ethanol, but when recrystallized first from petroleum (b.p. 80–100°) and then aqueous ethanol (charcoal) gave the arsine in colorless crystals, m.p. 88°; 2.45 g., 10%.

Anal. Calc'd for $C_{16}H_{18}AsN_2$: C, 62.3; H, 4.25.

Found: C, 62.1; H, 4.4.

Dihydrochloride. The arsine (0.3 g.) dissolved readily in an ice-cold saturated ethanolic hydrogen chloride solution. The latter was evaporated in a desiccator, and the brown syrupy residue readily crystallized when stirred with ether. The crystals when dissolved in ethanol and reprecipitated with acetone, and finally dried in a vacuum over sodium hydroxide, gave the arsine dihydrochloride, colorless crystals, m.p. 146–147°.

Anal. Calc'd for $C_{16}H_{18}AsN_2 \cdot 2HCl$: Cl, 18.6. Found: Cl, 18.4.

Dipicrate. A solution of the arsine (0.2 g.) and picric acid (1 g., 7 moles) in hot ethanol (20 cc.) when allowed to cool deposited a yellow oil which on scratching readily crystallized. These crystals of the dipicrate on being heated melted between 50° and 55°, appeared to resolidify, and then remelted at 136–142°; when recrystallized from ethanol containing a small quantity of acetone, they melted sharply at 142–143° without previous change; analysis indicated that their composition was unchanged.

Anal. Calc'd for $C_{16}H_{18}AsN_2 \cdot 2C_6H_3N_3O_7$: C, 43.85; H, 2.5; N, 14.6.

Found (before recrystallization): C, 43.6; H, 3.1.

(after recrystallization): C, 43.0; H, 2.5; N, 14.35.

Action of methyl iodide. (b) A solution of the arsine (0.3 g.) in methyl iodide (5 cc., 80 moles) was refluxed for 4 hours; during this period an oil which initially separated ultimately crystallized. The excess of methyl iodide was evaporated, and the residue, after two recrystallizations from ethanol containing ca. 3% of water, gave the *dimethiodide* as bright yellow crystals, m.p. 193–195° (dec.).

Anal. Calc'd for $C_{11}H_{11}AsI_2N_2$: C, 36.5; H, 3.2.
Found: C, 36.9; H, 3.6.

This dimethiodide was converted in the usual way into the *dimethopicrate*, yellow crystals from ethanol containing a small quantity of acetone; m.p. 190–191° (dec., with preliminary softening).

Anal. Calc'd for $C_{20}H_{22}AsN_2O_{14}$: C, 45.3; H, 2.9.
Found: C, 45.2; H, 3.1.

(d) A mixture of the arsine (0.3 g.), methanol (0.3 cc.), and methyl iodide (0.4 cc., 6.5 moles) was heated at 100° for 7 hours in a sealed tube. The dark red oily residue readily solidified, and when recrystallized as above furnished the dimethiodide, m.p. 192–195° (dec.).

Anal. Found: C, 36.3; H, 3.0.

Tri- β -pyridylamine This was prepared essentially by the method of Wibaut and La Bastide (24); the amine after recrystallization from water had m.p. 130°. Wibaut and La Bastide give m.p. 130°.

Dihydrochloride A solution of the amine (0.5 g.) in ethanol (5 cc.) was added to a cold saturated ethanolic hydrogen chloride solution (50 cc.). The highly deliquescent white crystalline precipitate of the dihydrochloride was filtered off and rapidly transferred to a vacuum desiccator containing sodium hydroxide

Anal. Calc'd for $C_{15}H_{12}N_4 \cdot 2HCl$: N, 17.4; Cl, 22.1.
Found: N, 17.55; Cl, 22.5.

Monopicrate A solution of the amine (0.3 g.) and picric acid (2.5 g., 9 moles) in hot ethanol (50 cc.) on cooling deposited yellow crystals of the monopicrate, m.p. 147–148°, which after recrystallization from ethanol had m.p. 147.5–148.5°; a mixture of the two samples had m.p. 147–148°.

Anal. Calc'd for $C_{15}H_{12}N_4 \cdot C_6H_2N_2O_7$: C, 52.8; H, 3.1.
Found: C, 52.5; H, 3.2.

Wibaut and La Bastide (24) prepared this compound, m.p. 150–151°.

Action of methyl iodide. (b) When a solution of the amine (0.4 g.) in methyl iodide (5 cc., 50 moles) was boiled under reflux, yellow crystals rapidly separated. After 4 hours' refluxing, the crystalline product was collected, recrystallized from ethanol, and then treated in aqueous solution with sodium picrate. The yellow crystalline *monomethopicrate* was thus obtained, m.p. 130–131° after recrystallization from ethanol; its m.p. was unchanged by admixture with the sample described below.

(c) A solution of the amine (1 g.) in nitromethane (10 cc.) containing methyl iodide (5 cc., 20 moles) was heated at 50–53° for 48 hours, yellow crystals separating meanwhile. After cooling, the crystals (0.8 g.) were filtered off, and when recrystallized from methanol gave the yellow *dimethiodide*, m.p. 202° (effer., with some sintering at 193°); the m.p. is affected by the rate of heating.

Anal. Calc'd for $C_{17}H_{18}I_2N_4$: C, 38.3; H, 3.4.
Found: C, 37.9; H, 3.5.

The addition of ether to the nitromethane-methyl iodide filtrate gave a pale yellow precipitate of the monomethiodide, which (unlike the dimethiodide) was freely soluble in hot ethanol, from which it was recrystallized, m.p. 198.5° (effer., with softening at 190°).

Anal. Calc'd for $C_{13}H_{13}IN_4$: C, 49.2; H, 3.9.

Found: C, 49.55; H, 3.9.

Wibaut and La Bastide (24) prepared only this monomethiodide, m.p. 204–206°.

This monomethiodide was converted to the *monomethopicrate*, yellow crystals from ethanol, in which it was readily soluble: m.p. 130.5–131°.

Anal. Calc'd for $C_{23}H_{17}N_7O_7$: N, 20.0. Found: N, 19.8.

(d) A mixture of the amine (1 g.), methanol (0.7 cc.) and methyl iodide (1.2 cc., 5 moles) was heated in a sealed tube at 100° for 8 hours. The hard yellow crystals of the dimethiodide were washed with methanol and dried; m.p. 196° (dec.). They were recrystallized from methanol before analysis.

Anal. Calc'd for $C_{17}H_{15}I_2N_4$: N, 10.5; I, 47.7.

Found: N, 10.5; I, 48.3.

The dimethiodide was converted to the *dimethopicrate*, which was only slightly soluble in hot methanol, ethanol, or acetone but was freely soluble in hot water. After recrystallization from aqueous ethanol it was obtained as yellow crystals of the dihydrate, which melted slowly with effervescence over a range of 149–162°.

Anal. Calc'd for $C_{23}H_{22}N_{10}O_{14} \cdot 2H_2O$: C, 45.2; H, 3.4.

Found: C, 45.1; H, 3.9.

Tri-2-pyridylphosphine. This phosphine was prepared by the method of Davies and Mann (25); m.p. 115°. Davies and Mann give m.p. 113–114°.

Trihydrochloride. When a solution of the phosphine (0.4 g.) in hydrochloric acid (5 cc.) was added to an ice-cold saturated ethanolic hydrogen chloride solution, no solid material separated. The solution was therefore confined over solid sodium hydroxide in an atmospheric desiccator for 3–4 days, when colorless crystals of the trihydrochloride separated. These, drained and dried over sodium hydroxide, had m.p. 207.5–209.5° with slight preliminary softening.

Anal. Calc'd for $C_{15}H_{12}N_3P \cdot 3HCl$: Cl, 28.4. Found: Cl, 27.9.

Dipicrate. When a solution of the phosphine (0.25 g.) in ethanol (5 cc.) was added to one of picric acid (2 g., 10 moles) also in ethanol (40 cc.), yellow crystals of the dipicrate (0.66 g.) rapidly separated; m.p. 141–142°, increased to 142–143° by recrystallization from ethanol.

Anal. Calc'd for $C_{15}H_{12}N_3P \cdot 2C_6H_3N_3O_7$: C, 44.8; H, 2.5; N, 17.4.

Found (before recrystallization): C, 45.0; H, 2.6; N, 17.5.

(after recrystallization): C, 44.4; H, 2.8; N, 17.5.

Action of methyl iodide. (c) A solution of the phosphine (0.4 g.) in nitromethane (5 cc.) containing methyl iodide (3 cc., 32 moles) was maintained at 50–55° for 48 hours. The cold product was then mixed with ether, which precipitated a red oil. The ether was decanted off, and the red oil extracted with a small quantity of cold ethanol, which dissolved the greater part of the oil but left some crystalline material undissolved. The crystals were filtered off, and the ethanolic filtrate again treated with ether. The oil which was now precipitated could not be obtained crystalline; it was therefore dissolved in water and treated with aqueous sodium picrate. Yellow crystals of the *monomethopicrate monohydrate* were thus obtained, m.p. 157–158° after recrystallization from ethanol, unchanged by admixture with the preparation described below.

Anal. Calc'd for $C_{22}H_{17}N_9O_7P \cdot H_2O$: C, 50.2; H, 3.6.
Found: C, 49.9, 50.3; H, 3.6, 3.5.

The above crystalline material was dissolved in the minimum of cold ethanol, filtered and reprecipitated by the addition of ether. The colorless crystals, m.p. 190° , were soluble in water, in which they furnished ionic iodine; analysis indicated they were *di-2-pyridylmonomethylphosphine dimethiodide monohydrate*.

Anal. Calc'd for $C_{13}H_{17}I_2N_2P \cdot H_2O$: C, 30.95; H, 3.8.
Found: C, 30.6; H, 4.0.

(d) A mixture of the phosphine (0.8 g.), methanol (0.5 cc.), and methyl iodide (0.8 cc., 4.3 moles) was heated in a sealed tube at 100° for 7.5 hours. The cold product formed a mass of yellow needles, which were washed with methanol, and thrice recrystallized from this solvent. Pale yellow crystals of 2,2'-dipyridyl dimethiodide, m.p. $239-242^\circ$ (dec.), were thus obtained.

Anal. Calc'd for $C_{12}H_{14}I_2N_2$: C, 32.7; H, 3.2; N, 6.35; I, 57.7.
Found: C, 32.9; H, 3.1; N, 5.95; I, 57.9.

It is noteworthy that during the first two recrystallizations from methanol, the hot solution was deep red but became yellow on cooling, but during the third recrystallization the solution was yellow throughout.

To confirm the identity of this dimethiodide, a portion was converted to the dimethopicate, which after recrystallization from acetone had m.p. $160.5-162^\circ$, unchanged by admixture with an authentic sample.

Tri-2-pyridylphosphine sulfide. This compound readily crystallized when a solution of the phosphine (0.85 g.) and sulfur (0.1 g., 1 atom) in benzene (20 cc.) was refluxed for 2 hours and allowed to cool. Recrystallization from ethanol gave colorless crystals, m.p. 161° .

Anal. Calc'd for $C_{18}H_{12}N_3PS$: C, 60.6; H, 4.1; N, 14.1.
Found: C, 61.2; H, 4.4; N, 14.0.

Monopicate. A solution of the sulfide (0.3 g.) and picric acid (2 g., 8 moles) in hot ethanol (40 cc.) on cooling deposited yellow needles of the monopicate, m.p. $156-158^\circ$, increased to $158-159^\circ$ by recrystallization from ethanol, and not affected by admixture with the original sample.

Anal. Calc'd for $C_{18}H_{12}N_3PS \cdot C_6H_3N_3O_7$: C, 47.9; H, 2.9; S, 6.1.
Found: C, 48.1; H, 2.7; S, 6.3.

Action of methyl iodide. (b) A solution of the sulfide (0.35 g.) in methyl iodide (20 cc., 275 moles) was refluxed for 7 hours. A brown syrup separated, and later changed to yellow crystals. The cold solvent was decanted, and the crystals dissolved in ethanol; addition of ether precipitated the yellow crystalline *monomethiodide*, m.p. $156-157^\circ$ (dec.).

Anal. Calc'd for $C_{16}H_{15}IN_3PS$: N, 9.6; I, 28.9.
Found: N, 9.4; I, 28.2.

An aqueous solution of this monomethiodide when treated with sodium picrate gave the *monomethopicate*, yellow crystals from ethanol, m.p. $208-211^\circ$ (effer.), unchanged by admixture with the sample described below.

(c) A solution of the sulfide (0.4 g.) in nitromethane (5 cc.) containing methyl iodide (3 cc., 36 moles) was maintained at 50° for 48 hours. The cold solution was poured into much ether, which precipitated a viscous brown gum; the ether was decanted, and the gum extracted with cold ethanol. After filtration of the extract, the gum was reprecipitated by the addition of ether. Since however the gum could not be induced to crystallize, it was dissolved in water and treated with sodium picrate. The monomethopicate was precipitated, yellow crystals from ethanol, m.p. $209-211^\circ$ (dec.)

Anal. Calc'd for $C_{22}H_{17}N_6O_7PS$: C, 48.9; H, 3.2.
Found: C, 48.6; H, 3.3.

(d) A mixture of the sulfide (0.5 g.), methanol (0.3 cc.) and methyl iodide (0.5 cc., 4.8 moles) was heated in a sealed tube at 100° for 7 hours. The yellow crystalline product was washed with cold methanol, and twice recrystallized from methanol containing a small proportion of water. The product, which was sulfur-free, decomposed *ca.* $219-222^\circ$; when however its aqueous solution was treated with sodium picrate it gave 2,2'-dipyridyl dimethopicate, m.p. $157-159^\circ$ after solution in acetone and reprecipitation with ether. The m.p. was unchanged by admixture with an authentic sample.

The united aqueous methanol mother-liquors slowly deposited yellow crystals; these, recrystallized from aqueous methanol, gave pure 2,2'-dipyridyl dimethiodide, m.p. $244-246^\circ$ (dec.).

Anal. Calc'd for $C_{12}H_{14}I_2N_2$: I, 57.7. Found: I, 58.0.

The united mother liquors were evaporated, but the residual red oil could not be crystallized. Its cold aqueous solution was therefore treated with aqueous sodium picrate; this gave an immediate yellow precipitate (A), and after filtration the solution slowly deposited more yellow crystals (B).

The compound (A) after recrystallization from methanol had m.p. $209-210^\circ$ (dec.) unaffected by further recrystallization, but depressed to $186-193^\circ$ (dec.) by admixture with the sulfide monomethopicate. Its identity remains uncertain.

Anal. Found: C, 38.0; H, 2.5; N, 17.3.

The crystals (B) were recrystallized first from methanol and then from ethanol, the m.p. $145-147^\circ$ being then unaffected. Analysis indicated that they were *mono-2-pyridyldimethylphosphine sulfide monomethopicate*.

Anal. Calc'd for $C_{14}H_{16}N_4O_7PS$: C, 40.6; H, 3.65; N, 13.5.
Found: C, 40.8; H, 3.2; N, 13.9.

Tri-2-pyridylphosphine oxide. Aqueous hydrogen peroxide (20 cc., "20 vols") was added to a solution of the phosphine (0.9 g.) in acetone (8 cc.), the mixture becoming slightly warm and cloudy. After 5 days the solvent was removed in a vacuum. The colorless residual crystals of the oxide were recrystallized from ethanol, m.p. 209° .

Anal. Calc'd for $C_{15}H_{12}N_3OP$: C, 64.1; H, 4.3; N, 14.9.
Found: C, 64.4; H, 4.4; N, 15.15.

Action of methyl iodide. A mixture of the oxide (0.44 g.), methanol (0.3 cc.), and methyl iodide (0.5 cc., 5 moles) was heated in a sealed tube at 100° for 7 hours. The cold yellow crystalline product, when recrystallized from methanol, gave 2,2'-dipyridyl dimethiodide, m.p. $243-245^\circ$ (dec.).

Anal. Found: I, 57.7.

For further identification, this compound was converted to the dimethopicate, yellow crystals from acetone, m.p. $160.5-162^\circ$, unchanged by admixture with an authentic sample.

Action of Chloramine-T on tri-2-pyridylphosphine. (A) When solutions of the phosphine (1 g.) and of Chloramine-T (1.01 g., 1 mole), each in hot aqueous ethanol (10 cc.) were mixed, sodium chloride was at once precipitated. The mixture was refluxed for 1.5 hours, filtered, cooled, and taken to dryness in a desiccator. The oily residue, which crystallized on scratching, was dissolved in boiling water (20 cc.), and the solution on cooling deposited colorless crystals of *p*-toluenesulfonamide, m.p. 135° , alone and mixed.

The aqueous filtrate was divided into two portions. One portion when treated with aqueous sodium picrate gave yellow crystals of the *phosphine oxide monopicrate*, m.p. $144-148^\circ$ after recrystallization from water.

Anal. Calc'd for $C_{11}H_{12}N_3OP \cdot C_6H_4N_3O_7$: C, 49.4; H, 2.9; N, 16.5.

Found: C, 49.7; H, 3.1; N, 16.9.

The second portion was evaporated, and the solid residue first extracted with boiling ether to remove *p*-toluenesulfonamide, and then recrystallized in turn from diethyl carbonate and from ethanol. Colorless crystals of the phosphine oxide were thus obtained, m.p. 207–209°, alone and mixed.

It is reasonably certain therefore that the original oily residue which crystallized was the hydroxyphosphine-*p*-toluenesulfonamide, $[(C_6H_4N)_3POH]NHSO_2C_6H_7$.

(B) When the condensation was repeated using anhydrous Chloramine-T in absolute ethanol, the crystalline residue when recrystallized from ethanol gave colorless crystals of *tri-2-pyridylphosphine-p-toluenesulfonylimine*, $(C_5H_4N)_3P \rightarrow NSO_2C_6H_7$, m.p. 177°.

Anal. Calc'd for $C_{22}H_{19}N_4O_2PS$: C, 60.9; H, 4.6; N, 12.9.

Found: C, 60.8; H, 4.4; N, 12.9.

Tri-2-pyridylarsine. This arsine, m.p. 85–85.5°, was prepared by the method of Davies and Mann (25), who give m.p. 85°.

Trihydrochloride. This salt was prepared precisely as that of the corresponding phosphine. Consistent m.p.'s. could only be obtained by preheating the immersion bath to within *ca.* 10° of the m.p. and then raising the temperature at a fixed rate (2° per minute). M.p. 145.5–146.5° (dec.). When a solution of this salt in conc'd aqueous hydrochloric acid was poured into an excess of ethanolic hydrogen chloride, the white crystals of the salt were reprecipitated, m.p. 152° (dec.).

Anal. Calc'd for $C_{15}H_{12}AsN_3 \cdot 3HCl \cdot Cl$: Cl, 25.4; N, 10.0.

Found: Cl, 25.3; N, 10.0.

Dipicrate. Prepared similarly to that of the corresponding phosphine; yellow crystals, m.p. 152–153° (dec.), unchanged by recrystallization from ethanol; mixed m.p. of products before and after recrystallization, unchanged.

Anal. Calc'd for $C_{14}H_{12}AsN_3 \cdot 2C_6H_3N_3O_7$: C, 42.2; H, 2.35; N, 16.4.

Found: C, 42.4; H, 2.35; N, 16.7.

Action of methyl iodide. (a) A solution of the arsine (0.6 g.) in benzene (15 cc.) containing methyl iodide (2.2 cc., 18 moles) was refluxed for 4.5 hours. The cold solvent was decanted from the crystalline deposit, which when twice recrystallized from much ethanol (*ca.* 300 cc.) gave yellow crystals of the *dimethiodide monohydrate*. The m.p. depended on the rate of heating, owing to preliminary decomposition; values of 186° and 194° were recorded.

Anal. Calc'd for $C_{17}H_{18}AsI_2N_3 \cdot H_2O$: C, 33.4; H, 3.3.

Found: C, 33.7; H, 3.3.

When heated for 6 hours at 120°/15 mm., this compound gave the anhydrous *dimethiodide*, m.p. 213–215° (dec.).

Anal. Calc'd for $C_{17}H_{18}AsI_2N_3$: N, 7.1; I, 42.8.

Found: N, 7.1; I, 43.4.

(b) A solution of the arsine (0.3 g.) in methyl iodide (5 cc., 83 moles) was refluxed for 4 hours; the brown oil which rapidly separated crystallized during the heating. The methyl iodide was evaporated, and the residue when recrystallized from aqueous ethanol gave the above *dimethiodide monohydrate*, m.p. 183–193° (dec.).

Anal. Found: C, 32.6; H, 3.7.

A portion was converted to the *dimethopicrate*, yellow crystals from water, m.p. 180–182° (dec.).

Anal. Calc'd for $C_{23}H_{22}AsN_3O_{14}$: C, 43.8; H, 2.8.

Found: C, 44.3; H, 2.9.

(c) A solution of the arsine (0.5 g.) in nitromethane (5 cc.) containing methyl iodide (3 cc., 30 moles) was heated at 47–53° for 48 hours. The yellow crystals which separated were recrystallized from aqueous ethanol and furnished the above dimethiodide monohydrate, m.p. 188–197° (dec.).

Anal. Found: C, 33.1; H, 3.2.

(d) A mixture of the arsine (0.6 g.) and methyl iodide (2.5 cc., 21 moles) was heated in a sealed tube at 100° for 8 hours. The cold methyl iodide was decanted from a residual brown glass, which when twice recrystallized from aqueous ethanol, furnished the *trimethiodide*, m.p. 201.5–204.5° (dec.).

Anal. Calc'd for $C_{18}H_{21}AsI_3N_3$: C, 29.4; H, 2.9; N, 5.7; I, 51.8.

Found: C, 30.0; H, 3.3; N, 5.7; I, 51.1.

Action of Chloramine-T on tri-2-pyridylarsine. Solutions of the arsine (0.7 g.) and the hydrated Chloramine-T (0.8 g.), each in hot ethanol (15 cc.) were mixed, and refluxed for 1 hour. Precipitated sodium chloride was filtered off, and the filtrate evaporated. The semi-solid residue solidified immediately it was stirred with cold water. The colorless crystals proved to be *p*-toluenesulfonamide, m.p. 136–137°. The aqueous extract contained the arsine oxide, for treatment with aqueous picric acid precipitated large yellow needles of the *arsine oxide monopicrate*, m.p. 144–147° with preliminary softening.

Anal. Calc'd for $C_{15}H_{12}AsN_3O \cdot C_6H_4N_2O_7$: C, 45.5; H, 2.7; N, 15.2.

Found: C, 45.4; H, 2.9; N, 15.3.

2,2'-Dipyridyl dimethiodide and dimethopicrate. Authentic samples of these compounds were required for direct comparison with the products arising in our work. The dimethiodide was made by the method of Blau (36), a mixture of 2,2'-dipyridyl (0.5 g.), methanol (0.25 cc.), and methyl iodide (0.5 cc., 2.5 moles) being heated in a sealed tube at 100° for 2 hours. The cold product formed yellow crystals, which when recrystallized from aqueous methanol had m.p. 237° (dec.). No m.p. is given by Blau (36).

When hot aqueous solutions of the dimethiodide and of an excess of sodium picrate were mixed and allowed to cool, an orange oil separated and ultimately solidified. Recrystallization from acetone gave the pure dimethopicrate, yellow crystals, m.p. 161.5–163°.

Anal. Calc'd for $C_{24}H_{18}N_6O_{14}$: C, 44.85; H, 2.8.

Found: C, 45.1; H, 2.9.

Attempted reduction of tri-2-pyridylamine. A mixture of the amine, (1 g.) granulated tin (10 g.), and concentrated hydrochloric acid (10 cc.) was warmed until vigorous effervescence occurred, and then more hydrochloric acid (40 cc.) added in small quantities at intervals over a period of 3 hours to maintain the reaction. The mixture was then refluxed for 1 hour, and much of the free acid finally removed by evaporation on a water-bath. The cold, almost solid product was treated with an excess of 30% aqueous sodium hydroxide and thrice extracted with benzene. The solvent was evaporated from the united dried benzene extracts, and the residue, when recrystallized from water, gave di-2-pyridylamine, m.p. 94–95°, unchanged by admixture with an authentic sample. Wibaut and La Bastide (24) give m.p. 95.5–96°.

Anal. Calc'd for $C_{10}H_8N_2$: C, 70.2; H, 5.25; N, 24.6.

Found: C, 70.4; H, 5.1; N, 25.1.

2-Methyldihydro-1,3-thiazine methiodide. This compound has hitherto been obtained only as an unanalyzed oil (18). When the thiazine (XIV) (1.1 g.) was dissolved in methyl iodide (4.1 g., 3 moles) in a closed flask, solid material began to separate within a few minutes. The mixture was set aside overnight, and then refluxed for 1 hour. The excess of methyl iodide was evaporated, and the residue when washed with ether gave the yellow

semi-solid deliquescent methiodide (2.2 g., 82%). The latter when twice recrystallized from ethanol gave pale yellow crystals, which after drying over phosphoric anhydride in a vacuum had m.p. 154–156° in a sealed tube.

Anal. Calc'd for $C_6H_{11}INS$: I, 49.4. Found: I, 49.9.

SUMMARY

1. Theoretical considerations are put forward to explain the fact that in many polyamines, not all the amino groups can exert simultaneously their normal reactivity towards acids, and—in the case of tertiary amines—towards alkyl halides. It is suggested that the positive pole created by the initial salt formation exerts a strong electronic attraction, and this attraction, relayed by the inductive or mesomeric effect, may virtually immobilize the lone pair of electrons on a neighboring nitrogen atom and so deactivate this atom. In certain cases, the cumulative effect of more than one positively charged atom may be required to exert this deactivating effect on a particular atom, depending on the nature of the molecule concerned. The same effect is observed in the reactivity of tertiary polyphosphines and arsines towards alkyl halides.

2. The theory is applied successfully to explain the reactivity towards acids and alkyl halides of mono-2-pyridyldiphenyl-amine, -phosphine, and -arsine, di-2-pyridylmonophenyl-amine, -phosphine, and -arsine, tri-2-pyridyl-amine, -phosphine, and -arsine and of certain of their derivatives.

CAMBRIDGE, ENGLAND

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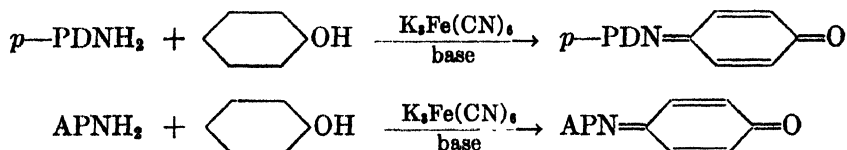
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THE CONDENSATION OF AMINOANTIPYRINE. VI. A STUDY OF THE EFFECT OF EXCESS BASE ON THE REACTION OF AMINOANTIPYRINE WITH PHENOLIC COMPOUNDS IN THE PRESENCE OF OXIDIZING AGENTS

EDGAR EMERSON¹ AND KENNETH KELLY²*Received February 10, 1948*

Previous work (1) has shown that potassium ferricyanide in basic solutions oxidizes a mixture of phenol and aminoantipyrine to a dye. This reaction appears to be analogous to the reactions of the *p*-diamines with phenols in which indophenols (2) are formed. If *p*-PDNH₂ is used to represent *p*-phenylenediamine and APNH₂ is used for aminoantipyrine the analogy of the reactions may be shown by the following equations:



It was recognized that this reaction of aminoantipyrine could be used as a test for certain phenolic compounds. During the course of earlier work it was noted that the tests for some phenols were erratic and led to results in variance with those already in the literature. This variance (3) of the results of the tests was particularly outstanding with solutions of *o*- and *m*-nitrophenol, and it was suspected that the amount and kind of base used produced an inhibiting effect on the reaction. The work reported in this paper was, therefore, undertaken with the object of determining this inhibiting effect and also of determining the most satisfactory base to use for general testing.

The inhibiting effect of excess base has been studied by comparison of the intensity of the colors developed in phenol solutions of various degrees of basicity. Solutions of aminoantipyrine, the oxidant, potassium ferricyanide, and the four bases, sodium bicarbonate, sodium carbonate, ammonium hydroxide, and sodium hydroxide were prepared in such a way that the first drop of the basic solution supplied the theoretically required quantity. Solutions of the phenolic compounds were used in concentrations of 1:10,000.

DISCUSSION

In general the condensations of phenolic compounds with aminoantipyrine are inhibited to a greater or lesser degree by excess base. The reactions of the nitrophenols and barbituric acid with aminoantipyrine are extremely sensitive to excess base, whereas solutions of β -naphthol are quite insensitive to an excess of

¹ Present address, 8 Beverly Road, West Hartford, 7, Conn.² Present address, Pratt & Whitney Aircraft, East Hartford, Connecticut.

base in these reactions. On the other hand, reactions with compounds such as α -naphthol and phenol exhibit an abnormal behavior. It will be noted that when α -naphthol is tested in the presence of sodium hydroxide there is a pronounced increase in the intensity of the color between four and five drops of base, and while it is not indicated in the table this increase is maintained even in the presence of ten drops. Between five and ten drops of sodium carbonate solution

TABLE I
EFFECT OF EXCESS BASES ON THE CONDENSATION REACTION OF PHENOLS WITH
AMINOANTIPYRINE^a

BASE	NaHCO ₃					Na ₂ CO ₃					NH ₄ OH					NaOH				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
<i>Compounds tested</i>																				
Barbituric acid	3 ^b	3	3	2	2	3	1	-	-	-	3	1	-	-	-	1	-	-	-	-
<i>o</i> -Chlorophenol	5	5	5	5	5	5	5	5	5	3	5	5	5	5	5	5	2	1	-	-
2,6-Dibromophenol . . .	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	1	-	-	-
<i>m</i> -Hydroxybenzoic acid	1	2	2	2	2	3	3	3	2	2	3	3	3	3	2	2	1	1	1	1
5-Hydroxy-1,3-dimethyl- benzene	3	4	4	2	2	3	2	2	2	2	1	3	3	2	2	3	2	2	2	2
8-Hydroxyquinoline	5	5	5	5	5	5	5	5	5	2	5	5	5	5	5	5	5	5	1	1
α -Naphthol	5	5	5	5	5	5	2	2	2	2	2	2	2	2	2	2	2	2	2	5
β -Naphthol	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
<i>o</i> -Nitrophenol	3	3	3	3	2	3	-	-	-	-	3	-	-	-	-	-	-	-	-	-
<i>m</i> -Nitrophenol	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Phenol	3	3	2	2	2	3	3	2	2	2	3	3	3	3	3	3	3	2	1	1
Phloroglucinol	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	-
1-Phenyl-3-methylpyra- zolon-5	3	3	3	3	3	3	3	2	2	1	3	3	2	2	2	2	-	-	-	-
Salicylic acid	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2,4-Dichlorophenol . . .	5	5	5	5	5	5	5	3	3	2	5	5	3	3	3	2	1	-	-	-
<i>p</i> -Hydroxybenzoic acid	2	3	3	2	2	3	2	2	2	2	3	3	3	3	2	2	2	1	1	1
2,4,6-Tribromophenol	5	5	5	5	5	5	5	1	1	1	5	5	1	1	1	5	-	-	-	-

^a Most of the colors developed in the test solutions range from yellow-orange to red, but 5-hydroxy-1,3-dimethylbenzene produces a purple solution, β -naphthol a green solution, and phloroglucinol a yellow-brown to brown-red solution.

^b The numbers used to designate the intensity of the colors developed are arbitrary: 1 indicates a weak test, 4 a very intense test, and 5 indicates the formation of a precipitate.

there is produced a similar effect on α -naphthol and phenol, although in the case of phenol the increase is not so pronounced. The decrease in the intensity of the test with excess base is not due to the dilution of the test solution.

In cases where the reaction is carried out at the threshold of sensitivity the dilution factor may be important. For salicylic acid this threshold is 1:10,000 and it will be noted in the table that this compound fails to give the test in all but the lowest concentrations of sodium bicarbonate. However, solutions of salicylic acid, 1:1,000, develop the most intense color in a solution of sodium hydroxide. This behavior is noted in an as-yet-undetermined constituent of urine.

While the reaction of 2,6-dibromophenol with aminoantipyrine is rather insensitive to excess base, the reaction of 2,4,6-tribromophenol displays a pronounced sensitivity when the stronger bases are used. It has been observed in this laboratory that condensations of compounds which have a group or atom expelled during the reaction are inhibited more by excess base than condensations of the parent compounds.

It was found that the bases, when used in excess, can be arranged in a series of increasing inhibiting effect: sodium bicarbonate < ammonium hydroxide < sodium carbonate < sodium hydroxide. This series is remarkably similar to that reported previously (4) for the efficiency of bases in promoting those coupling reactions which are accompanied by expulsion. The reaction of aminoantipyrine with a phenolic compound is best accomplished in a sodium bicarbonate solution in which slight variations in the amount of base will have the least retarding effect.

EXPERIMENTAL

The aqueous solutions for the tests reported in this paper were prepared as follows:—phenolic compound 0.100 g./l.; $K_3Fe(CN)_6$ 54.2 g./l.; aminoantipyrine 8.47 g./l.; $NaHCO_3$ 14.0 g./l.; Na_2CO_3 8.8 g./l.; conc'd NH_4OH 11.25 cc. diluted to one liter; $NaOH$ 6.67 g./l.

To 2 cc. of the phenolic solution in a 100 × 10 mm. test tube was added the requisite quantity of base followed by one drop of the aminoantipyrine solution. After the solutions were well mixed one drop of the oxidant was added and the test tube shaken for fifteen seconds. This shaking is necessary for the formation of a precipitate in many cases. After 3 to 5 minutes the color of the solution was noted.

The dropping tubes were standardized to deliver a drop of 0.04 cc.

SUMMARY

The condensation reaction of aminoantipyrine has been shown to be sensitive to bases. The order of interference is sodium bicarbonate < ammonium hydroxide < sodium carbonate < sodium hydroxide. It is recommended that sodium bicarbonate be used as the base for the aminoantipyrine test because excesses of this reagent have the least retarding effect on the reaction.

[WEST HARTFORD, CONN.]

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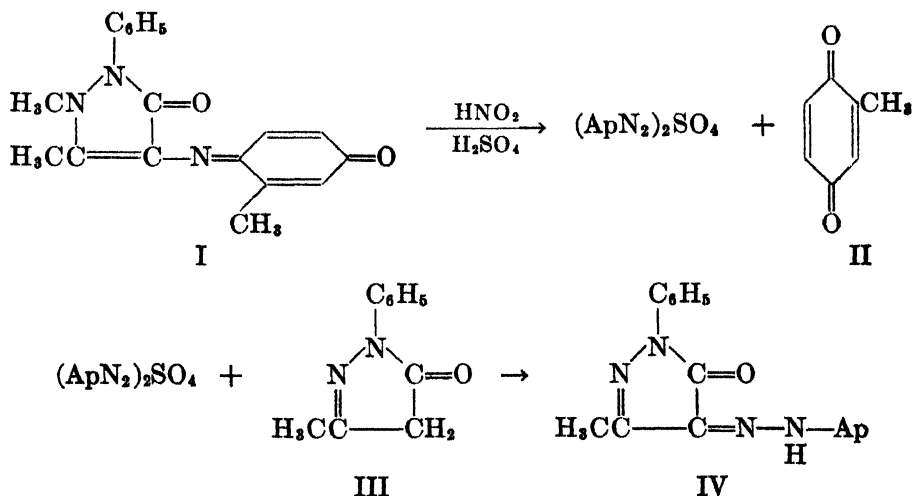
THE CONDENSATION OF AMINOANTIPYRINE. VII. HYDROLYSIS
IN THE PRESENCE OF NITROUS ACID (1)¹EDGAR EMERSON² AND JOHN SAGAL*Received February 10, 1948*

In the course of investigating the structure of some indophenol-type dyes formed by the interaction of 4-aminoantipyrine with phenols, difficulty was experienced in isolating the hydrolytic products. These products, 4-aminoantipyrine and quinone, react with each other at once to form anils in the same manner as aniline and quinone react.

It was thought that if the amine could be precipitated or otherwise removed from the reaction mixture as fast as it was formed during the hydrolysis, then the quinone could be isolated after the completion of the reaction. The presence of mercuric chloride, picric acid, or chloroplatinic acid failed to prevent anil formation.

Knorr (2) in 1896 reported that the diazonium salts of 4-aminoantipyrine were stable in hot aqueous solutions, and he also prepared and characterized a number of diazonium dyes made from aminoantipyrine. With these facts in mind, the hydrolysis of the antipyrin-indophenol dyes was carried out in the presence of sulfuric acid and nitrous acid. Apparently the amine liberated during the hydrolysis diazotizes faster than it reacts with the liberated quinone, because there is no apparent anil formation and because azo derivatives can be isolated in 94–95% yield and the pure quinone in 51% yield. While the yield of the quinone is low it is not inconsistent with quinone yields obtained by other methods.

A typical reaction may be summarized as:



where Ap is the antipyrinyl radical.

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² Present address, 8 Beverly Road, West Hartford, Connecticut.

STEROLS OF MARINE MOLLUSKS. I. THE PRESENCE OF CHOLESTEROL IN TWO GASTROPODS¹

C. ALBERT KIND, SCHUYLER G. SLATER, AND ANN VINCI

Received February 17, 1948

Recent investigations of the sterols of marine invertebrate animals have provided valuable information regarding the types of structures one may expect to find in the naturally occurring members of this class of compounds. Of particular significance is the occurrence of such C_{28} sterols as stellasterol and stellastenol (1), neospongosterol (2), and chalinasterol (3). The latter compound is likely to prove of considerable importance in studies of the comparative biochemistry of marine life, since evidence has been offered to indicate that chalinasterol is identical with ostreasterol isolated by Bergmann from bivalves in 1934 (4). Bergmann and Low (5) have called attention to the apparent quantitative differences in sterol content within the phylum *Mollusca*. They have postulated that the gastropods may be characterized by the presence of cholesterol as the principal sterol, whereas the pelecypods may be expected to contain ostreasterol-like compounds.

We have investigated the sterol fraction of two gastropods, the *Nassa obsoleta* common to the New England coast, and the *Nerita peleronta* obtainable from the coastal waters of Florida, Bermuda, and the West Indies. In both cases the isolation of cholesterol as the principal sterol supports the suggestion offered by Bergmann and Low.

The specimens of *Nassa obsoleta* were obtained from the Marine Biological Laboratory at Woods Hole, Massachusetts, and were found to contain 0.27% of nonsaponifiable matter. When this material was treated with hot methanol and cooled to room temperature, a hydrocarbon fraction was precipitated. This fraction upon crystallization from methanol yielded a product melting at 59–60°, which we presume to be heptacosane. When the filtrate was cooled to 5°, a second precipitate was obtained which gave typical color reactions for sterols. The crude sterol fraction was crystallized repeatedly from ethanol, giving a product melting at 132–139°. Attempted purification through the digitonide yielded a material of somewhat higher melting point (138–141°). When this material was acetylated and treated with bromine in glacial acetic acid, an acetate dibromide was precipitated, m.p. 110–112°, which gave no depression with cholesteryl acetate dibromide. The small yield obtained by the bromination procedure, and the fact that several samples decomposed on standing, led to attempts to separate the sterol mixture by fractional crystallization of a derivative. After unsuccessful efforts to fractionate either the steryl bromides or the acetates, advantage was taken of the insolubility of cholesteryl benzoate. Benzoylation of the mixture gave a product the bulk of which proved to be very difficultly soluble in 95% ethyl alcohol. Repeated crystallizations from absolute

¹ This study was aided by a grant from the University of Connecticut Research Fund.

alcohol yielded cholesteryl benzoate as the least soluble fraction. The filtrates contained a benzoate melting at 130–132°, which could not be identified due to lack of material. An investigation now in progress in this laboratory suggests that this lower-melting benzoate may be clionasteryl benzoate (m.p. 134–135°). The presence of clionasterol has not been demonstrated in mollusks as far as the authors are aware.

Specimens of the *Nerita peleronta*, commonly known as the “bleeding tooth”, were obtained from Bermuda through the courtesy of Prof. Werner Bergmann of Yale University. The tissue contains about three and one-half per cent of acetone-ether soluble material. The nonsaponifiable matter consists of about ten per cent sterol, identified as cholesterol through the preparation of the acetate and benzoate. No evidence was found for the presence of other sterols in the *Nerita*.

EXPERIMENTAL

*Nassa obsoleta*²

Isolation of the nonsaponifiable matter. The specimens of this mollusk had been collected over a period of several weeks and preserved in ethyl alcohol. The material, weighing 15.6 kg., was placed in a mechanical grinder and shell and tissue were ground together. The finely ground mass was filtered and without further drying was divided into four batches of approximately 4 kilograms each. All batches were dehydrated by extraction with acetone in a Soxhlet apparatus and then exhaustively extracted with ether. The solvents were removed and the extracts saponified. The nonsaponifiable fraction was obtained as a yellow-brown crystalline solid weighing 42.5 g. or 0.27% of the wet weight.

Separation of the sterol fraction. Ten grams of the nonsaponifiable matter was dissolved in 50 cc. of boiling methanol. On cooling to room temperature, a light yellow mass of amorphous material precipitated (Fraction A). This was filtered and the filtrate cooled at 5° for 12 hours, during which time a white crystalline precipitate had formed. This was also filtered and will be referred to as Fraction B. Fraction B gave positive Liebermann-Burchard and Salkowski tests whereas these tests were negative when applied to Fraction A. The melting points of Fractions A and B were 52–60° and 118–131° respectively.

The mother liquor remaining after the removal of the above fractions contained a dark brown oil which could not be crystallized. Attempts to purify this material by distillation and chromatographic adsorption were unsuccessful, and investigation of this mixture has been temporarily abandoned.

Fraction A. This material, constituting about 5% of the nonsaponifiable matter, was crystallized twice from methanol and five times from acetone until the melting point had reached a constant value of 59.6–60.4°. It was optically inactive and gave negative tests for unsaturation. Heptacosane is reported as melting at 59.2° (6).

Anal. Calc'd for $C_{27}H_{54}$: C, 85.17; H, 14.83.

Found: C, 84.85; H, 14.99.

Fraction B. The crude material (m.p. 118–131°) weighed 0.950 g. or 9.5% of the nonsaponifiable matter. Repeated crystallizations from methanol gave 255 mg. of product melting at 132–139°. This material was dissolved in ethanol, 75 cc. of a 1% solution of digitonin was added, and the mixture heated to boiling. After standing at room temperature for 24 hours, the mixture was again heated to boiling and allowed to stand overnight. The digitonide was filtered, washed with cold ethanol, and dried. Eight hundred fifty-six milligrams was obtained, indicating the presence of 214 mg. of sterol. The digitonide was

² The authors wish to acknowledge the cooperation of Prof. John S. Rankin of the Department of Zoology, University of Connecticut in obtaining this material.

split by treatment with pyridine according to the method of Bergmann (7) and, after recrystallization from methanol, 151 mg. of sterol was obtained melting at 138–141°; $(\alpha)_D^{25} -32.6^\circ$ (44.2 mg. in 3 cc. of chloroform gave an α reading of -0.48°).

Preparation of the acetate bromide. The acetate of the impure sterol (m.p. 138–141°) was prepared in the usual manner, and melted at 121–123°. The acetate was brominated by the method of Windaus and Hauth (8) and a small yield of insoluble acetate dibromide was obtained. This material melted at 110–112° and gave no depression when mixed with cholesteryl acetate dibromide.

Anal. Calc'd for $C_{29}H_{48}Br_2O_2$: Br, 27.16.

Found: Br, 26.68.

Debromination of the acetate with zinc and acetic acid yielded cholesteryl acetate, m.p. 112–114°, which gave no depression of the melting point when mixed with authentic material.

Preparation of the benzoate. Four hundred fifty-six milligrams of sterol, prepared through the digitonide, was converted to the benzoate by treatment with benzoyl chloride in pyridine. The product was recrystallized from 95% ethyl alcohol, in which it was difficultly soluble. Repeated crystallizations from absolute alcohol, in which the material was more soluble, afforded two fractions. The less soluble fraction, representing about 80% of the mixture, melted to a turbid liquid at 145–147° and cleared at 175°; $(\alpha)_D^{25} -17.70^\circ$ (26.4 mg. in 3 cc. of chloroform gave an α reading of -0.15°). When mixed with cholesteryl benzoate no depression of the melting point was observed.

Anal. Calc'd for $C_{34}H_{50}O_2$: C, 83.21; H, 10.27.

Found: C, 82.63; H, 10.60.

Saponification of the benzoate gave cholesterol, m.p. 145–146°; $(\alpha)_D^{25} -38.2^\circ$ (21.2 mg. in 3 cc. of chloroform gave an α reading of -0.27°). There was no depression of the melting point when this material was mixed with authentic cholesterol.

The more soluble fraction of the benzoate mixture melted at 130–132°. Lack of material made identification of this fraction impossible.

Nerita peleronia

Soxhlet extraction of 533 g. of this mollusk with acetone and ether in the manner previously described yielded 18 g. (3.4%) of a dark brown viscous oil. The oil was saponified with 50 cc. of alcoholic potassium hydroxide, and the nonsaponifiable matter consisted of 3.2 g. of a light brown gummy mass mixed with large plate-like crystals. The mixture was treated repeatedly with boiling methanol, in which the gum was very slightly soluble. On cooling, the combined methanol solutions deposited a crystalline precipitate weighing 0.675 g. and melting at 139–143°. Ten crystallizations from methanol yielded 0.332 g. of sterol melting at 146–147° which gave no depression of the melting point when mixed with cholesterol; $(\alpha)_D^{25} -39.4^\circ$ (28.1 mg. in 3 cc. of chloroform gave an α reading of -0.37°).

Anal. Calc'd for $C_{27}H_{46}O$: C, 83.87; H, 11.99.

Found: C, 83.86; H, 12.02.

Acetylation of the sterol with acetic anhydride gave cholesteryl acetate, m.p. 113–114°. No depression of the melting point was observed when mixed with authentic material.

Cholesteryl benzoate. One hundred milligrams of sterol was converted to the benzoate by treatment with benzoyl chloride in pyridine. The product displayed the characteristic behavior of cholesteryl benzoate, melting to a turbid liquid at 146° and clearing at 177–178°. A mixed melting point with authentic cholesteryl benzoate showed no depression; $(\alpha)_D^{25} -16.1^\circ$ (36.4 mg. in 3 cc. of chloroform gave an α reading of -0.19°).

Anal. Calc'd for $C_{34}H_{50}O_2$: C, 83.21; H, 10.27.

Found: C, 82.98; H, 10.50.

SUMMARY

The nonsaponifiable matter of two gastropod mollusks, *Nassa obsoleta* and *Nerita peleronia*, has been investigated and cholesterol has been identified as the

principal sterol present in these animals. The presence of cholesterol in both cases has been established by comparison of the properties of the free sterol and several derivatives.

In addition, the nonsaponifiable matter of the *Nassa obsoleta* has been shown to contain considerable quantities of a hydrocarbon mixture, the major component of which is heptacosane.

The results of this investigation may be interpreted as supporting the suggestion that the sterols of mollusks are probably independent of the diet and that the gastropods contain cholesterol as the principal sterol.

STORRS, CONNECTICUT

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REGENERATION OF STEROID KETONES FROM THEIR SEMICARBAZONES WITH PYRUVIC ACID¹

E. B. HERSHBURG

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An important step in the separation of ketonic hormone intermediates obtained from the oxidation of sterols is the formation of their sparingly soluble semicarbazones. After suitable purification, the semicarbazones may be "split" by any one of several methods and the steroid ketones are thus recovered. Methods for accomplishing the split include treatment with strong acid, exchange with an excess of some other ketone or aldehyde in non-aqueous solution, and the recently described² nitrous acid in acetic acid procedure (1, 2, 3). The first two methods, which are in common use, are drastic and lead to significant amounts of irreversible condensation products or to partial hydrolysis of the acetylated hydroxyl groups which are often present.³

Conant and Bartlett (12) made a quantitative study of semicarbazone formation in which they confirmed earlier observations on reaction rates by Grassi (13, 14), and a statement made by Sidgwick (15) that pyruvic acid in aqueous medium is a particularly effective exchange ketone. They found that the hydrolysis constant of pyruvic acid semicarbazone has a low limiting value, resembling that of an aromatic aldehyde semicarbazone. A buffer action is also provided by the presence of carboxyl and amino groups in the same molecule which resists hydrolysis caused by changes in acidity.

In the new method described below, advantage is taken of the favorable properties of pyruvic acid and of its semicarbazone to effect an exchange in acetic acid solution with the semicarbazone moiety of the steroid ketones. Acetic acid is a particularly good solvent for this purpose. It is a good ionizing medium (16) for this reaction, and the steroid semicarbazones are very soluble in the anhydrous solvent and to a considerable extent even in dilute aqueous mixtures. This per-

¹ In a communication to the Editor, Mattox, and Kendall, *J. Am. Chem. Soc.*, **70**, 882 (1948), describe the use of pyruvic acid together with hydrobromic acid in chloroform solution to split methyl 3,11-diketo-12-bromo- Δ^4 -cholenate-3-(2,4-dinitrophenylhydrazine). Dr. Kendall first reported this work at the 112th Meeting of the American Chemical Society in New York, September, 1947.

² Upon repetition in this laboratory, the yield of crude dehydroisoandrosterone acetate recovered by this method was found to be practically quantitative as reported. However, its quality was poor and the melting point was from 5–10° low, even when a highly purified sample of semicarbazone was employed. In general, the results were not equal to those obtained by the pyruvic acid method.

³ Examples of the more common hydrolytic methods for splitting semicarbazones are illustrated in the following references; sulfuric acid in alcohol, (4, 5, 6, 7); sulfuric acid in dioxane, (8, 9); hydrochloric and acetic acids, (10). Oxalic acid, which was used by Ruzicka, Goldberg, Meyer, Brünnger, and Eichenberger (11) for the hydrolysis of the semicarbazones from the oxidation of epidihydrocholesterol acetate gave as a product the neutral oxalate ester of two molecules of androsterone.

mits an irreversible shift in the equilibrium, for it is often possible to crystallize the less soluble ketone from the reaction mixture of keto-steroid semicarbazone, pyruvic acid, and acetic acid, by adding water gradually to the refluxing solution. The ketone is thus removed from solution as it is formed, and the yields obtained are nearly quantitative. When the solubility relationships are not favorable, it is sufficient to reflux the solution of the reactants for a short time and then to add water until the saturation point of the ketone is reached. Upon slow cooling, the ketone usually crystallizes from the solution.

The reaction rate is several times greater when using pyruvic acid than with its sodium salt or in the presence of sodium acetate. This advantage is offset by the fact that pyruvic acid in acetic acid solution is a strong acid, approaching oxalic acid in strength, and causes from five to ten per cent hydrolysis of any acetyl protected hydroxyl groups in the molecule. To avoid this hydrolysis, it was found preferable to conduct the reaction in a solution buffered with sodium acetate. In carefully conducted experiments with dehydroisoandrosterone acetate semicarbazone and sodium pyruvate, 97% of the dehydroisoandrosterone acetate could be recovered, whereas the use of pyruvic acid alone resulted in a mixture from which about 92% of ketone acetate was obtained, and dehydroisoandrosterone was found in the mother liquors. When the ketone did not contain acid-sensitive groups it was advantageous to make use of the more rapid hydrolysis obtained with pyruvic acid. However, pyruvic acid semicarbazone is only moderately soluble in dilute acetic acid solution and, for example, in the exchange with cholestenone semicarbazone it sometimes crystallized together with the cholestenone. Under these conditions it was found that the addition of sodium acetate at the end of the reaction formed the more soluble sodium pyruvate semicarbazone and avoided contamination of the steroid ketone.

Oximes as a class are less useful in the separation of steroid ketones than the semicarbazones, for they are sometimes more soluble and often differ but slightly in properties from their parent ketones. Furthermore they are less readily hydrolyzed than semicarbazones and require longer treatment with pyruvic acid or its salt. A few examples have been included, however, for a general procedure is lacking.

Acknowledgment. The author wishes to express his appreciation to Dr. Erwin Schwenk for his helpful advice and criticism.

EXPERIMENTAL PART^{4, 5}

The experimental procedure developed for dehydroisoandrosterone acetate semicarbazone is typical and is reported in detail. The other ketones and diketones were selected to represent different types that might establish the generality of the method as completely as possible. Of necessity, the procedure must be adapted to the peculiarities of the ketone being recovered, its solubility, its ease of crystallization, and its initial purity.

A 50% molar excess of pyruvic acid over the semicarbazone was employed. At first, anhydrous pyruvic acid was used but it was later found that the small amount of water introduced by a 50% solution had a negligible effect. Technical pyruvic acid was carefully

⁴ All melting points are corrected.

⁵ Microanalyses were performed by Mr. Edwin Conner of this laboratory.

distilled in a vacuum without fractionation at a pressure of 5–10 mm. The aqueous product, adjusted by titration to a 50% by weight concentration, was stable, and did not discolor upon standing.

Dehydroisoandrosterone acetate. (a) *Semicarbazone exchange with sodium pyruvate.* To a solution of 10.00 g. of dehydroisoandrosterone acetate semicarbazone (m.p. 279.5–280.5° dec., inserted at 255°; prepared from dehydroisoandrosterone acetate m.p. 170.2–170.7°) in 30 cc. of glacial acetic acid warmed to 110° was added a solution consisting of 3.2 g. of anhydrous sodium acetate and 7.0 g. of a 50% by weight solution of aqueous pyruvic acid in 15 cc. of hot acetic acid. The second flask was rinsed with an additional 5-cc. portion of acetic acid which was added to the reaction flask. A small amount of semicarbazone separated at this point but redissolved after shaking for a few minutes. After 10 minutes at 105–110°, water was added dropwise until 15 cc. had been added and the solution was sufficiently dilute so that refluxing occurred below 110°. The dropwise addition of water was continued at a rate such that after about 25 minutes a total of 46 cc. of water had been added and the solution was saturated, so that upon seeding and slight cooling the ketone acetate began to crystallize. The boiling point of the solution was now 105° and the addition of water was continued at an increased rate while under reflux so that after an elapsed time of about 35 minutes from the beginning of the addition a total of 100 cc. of water had been added, and the solution was thick with crystalline product. Then the flask was set aside to cool slowly so that thick needles formed which permitted easy filtering and washing. After standing from one to two hours at room temperature, the flask was placed in the refrigerator to cool to 0° and the product was collected with suction, washed with ice-cold dilute acetic acid (25% by volume), and with water. Upon drying at 110° under vacuum for from 1–2 hours there was obtained 8.28 g. of dehydroisoandrosterone acetate (97.2%), m.p. 170.2–170.9°.

(b) *Semicarbazone exchange with pyruvic acid.* The following experiment illustrates the behavior of a typical acetate under the mildly hydrolytic conditions which exist when using pyruvic acid.

A suspension of finely divided solid was prepared by diluting a solution of 10.00 g. of dehydroisoandrosterone acetate semicarbazone in 50 cc. of hot acetic acid with 25 cc. of hot water. Thereupon 7.0 g. of 50% pyruvic acid was added and the suspension was heated to reflux. After 5 to 7 minutes the semicarbazone dissolved and the solution was refluxed for 10 minutes longer. Then 75 cc. of water was added over a 10-min. period and the flask was put in the refrigerator to cool slowly. After 2 hours the contents were at about 5° and the crystalline product was collected, washed twice with ice-cold dilute (25%) acetic acid and finally with water. After drying as before, there was obtained 7.90 g. (92.5%), m.p. 170.0–170.7°.

Dilution of the acetic acid mother liquors with water to a volume of about 900 cc. gave 0.42 g. of solid, m.p. 124–129°. This material which in other experiments was purified to give dehydroisoandrosterone m.p. 147.5–149.5°, (the m.p. of a mixture with authentic material was the same) was acetylated by boiling for 5 minutes with a few cc. of acetic anhydride and then crystallized directly by adding water dropwise to the boiling solution until saturation had been reached. There was obtained upon cooling 0.38 g. of acetate (4.5%), m.p. 168–170°.

Isoandrosterone. A suspension of 1.00 g. of the semicarbazone (m.p. 286–288° dec., prepared from isoandrosterone m.p. 170.5–172.5°) in 15 cc. of acetic acid, 15 cc. of water, 0.78 g. of 50% pyruvic acid, and 0.37 g. of sodium acetate was refluxed for 1 hr., when solution was complete. Then 20 cc. of water was added and upon slow cooling 0.65 g. of isoandrosterone m.p. 170–172.5° was obtained. Dilution of the mother liquor with several volumes of water gave an additional 0.11 g. with m.p. 169–172° (total 91%). Though the reaction was slow, better results were obtained in dilute acetic acid solution, possibly due to the easy acetylation of isoandrosterone in strong acetic acid with resulting contamination of the product by the lower-melting acetate.

Dihydrotestosterone. [Androstan-17(α)-ol-3-one. According to evidence recently

presented by Goldberg *et al.* (17) the actual configuration is (β). A solution of 0.75 g. of the semicarbazone [m.p. 261–262° dec., inserted at 255°, prepared from ketone m.p. 180.5–181.5°; Butenandt, Tscherning, and Hanish (18) report this semicarbazone with the m.p. 237–243° uncorr.] was dissolved in 5 cc. of acetic acid, 0.59 g. of 50% pyruvic acid and 0.28 g. of sodium acetate, and refluxed for one hour. After diluting with water to saturation and slow cooling and seeding, there was obtained 0.59 g. of product m.p. 175–179° (94%). Recrystallization from acetone-ligroin gave 0.52 g. (83%) of dihydrotestosterone, m.p. 180–181.5°.

Δ^5 -Pregnen-3-ol-20-one acetate semicarbazone (2.00 g., m.p. 265–266° dec., inserted at 257°; from pregnenolone acetate m.p. 142–148°) was warmed to boiling with 1.4 g. of 50% pyruvic acid, 0.64 g. of sodium acetate and 10 cc. of acetic acid. Over a one-half hour period 20 cc. of water was added dropwise, which resulted in saturation of the solution. Upon cooling and seeding there was obtained 1.70 g. (100%) of crystalline material, m.p. 145.5–148.5°. This was recrystallized from methanol to give 1.49 g. (88%) of glistening white leaflets, m.p. 147–149°.

Δ^5 -Norcholesten-3-ol-25-one acetate semicarbazone (2.00 g., m.p. 234–235° dec.) was refluxed for 10 minutes with a solution of 12 cc. of acetic acid, 3 cc. of water, 1.14 g. of pyruvic acid and 0.52 g. of sodium acetate. The solution was cooled to about 90°, whereupon glistening leaflets began to separate. More water was added dropwise and the solution was brought to a boil and refluxed. After 30 minutes a total of 17 cc. of water had been added, and upon cooling the suspension to 0°, collecting and drying, there was obtained 1.76 g. of ketone m.p. 138.5–141° (99%). Recrystallization from dilute acetic acid gave 1.70 g. (96%) of glistening white leaflets, m.p. 139.5–141°.

Δ^4 -Cholesten-3-one semicarbazone (5.00 g., m.p. 237–239° dec., inserted at 230°; prepared from cholestenone m.p. 79–80°) was suspended in a solution of 25 cc. of acetic acid, 3.1 g. of 50% pyruvic acid and 5 cc. of water and heated to reflux. After 10 minutes 25 cc. of water was added dropwise and the flask was then cooled in an ice-bath. The milky dilute acid layer was decanted from the viscous oil, which was treated with 50 cc. more of water and brought to a boil. After cooling, the oil slowly crystallized and the solid was collected, washed with water, and dried; 4.25 g. (97%), m.p. 80–86°. Recrystallization of 4.18 g. from acetone-methanol gave 3.81 g. (89%) of cream-colored prisms, m.p. 79–80°.

The dilute acetic acid mother liquors deposited pyruvic acid semicarbazone upon standing overnight, m.p. 121–122° dec.

Δ^4 -Androstene-3,17-dione disemicarbazone and its exchange. A 2.50-g. portion of androstenedione, m.p. 171.5–173°, dissolved in 15 cc. of boiling acetic acid was treated with a solution of 5.9 g. of semicarbazide hydrochloride and 5.1 g. of sodium acetate in 14 cc. of water. The disemicarbazone soon formed in a microcrystalline condition and the reaction was completed by warming the mixture for one hour on the steam-bath. In three successive experiments there was obtained 3.65 g. (91%), 3.81 g. (95%), and 3.88 g. (96.5%) of material with no definite melting point.

The product crystallizes with one molecule of acetic acid of crystallization as indicated by the following analysis:

Anal. Calc'd for $C_{21}H_{32}N_6O_2 \cdot CH_3COOH$: N, 18.25. Found: N, 17.99.

Androstenedione dioxime. A solution of 7.3 g. of sodium acetate and 4.9 g. of hydroxylamine hydrochloride dissolved in 30 cc. of water was added to a hot solution of 2.50 g. of androstenedione in 75 cc. of ethyl alcohol. The resulting clear solution was refluxed for 2.5 hours and then the concentration was adjusted by the addition of 75 cc. of water so that a crystalline precipitate was obtained upon cooling. After collecting, washing with 50% methanol, and drying there was obtained 2.64 g. (95%) of dioxime, m.p. 195–210°. The product is a mixture of isomers from which one could be separated after three successive recrystallizations from 50% ethyl alcohol and three more from methanol. It formed colorless rectangular prisms, m.p. 229–230° which became opaque upon drying at 100° for 3 hrs. *in vacuo*. Butenandt and Kudzus (19) report this compound with the melting point 143° (uncorr.).

Anal. Calc'd for $C_{15}H_{23}N_2O_2$: N, 8.86. Found: N, 9.00.

The exchange of 1.00 g. of dioxime, m.p. 195–210° in a refluxing solution of 5 cc. of acetic acid, and 10 cc. of water with 1.7 g. of pyruvic acid was complete in 50 min. Upon cooling, two crops of needle-shaped crystals were obtained: 0.60 g., m.p. 168–171°, and 0.11 g., m.p. 165–167° (total, 78%). Recrystallization of the combined material gave 0.61 g., m.p. 170–172°.

Progesterone dioxime. The dioxime was made in the usual way (yield, 94%) and formed a micro-crystalline powder which upon recrystallization from alcohol melted at 247–256° (20). Though it had the proper nitrogen content, it evidently was a mixture of isomers.

Anal. Calc'd for $C_{21}H_{32}N_2O_2$: N, 8.13. Found: N, 8.20.

The exchange of 0.30 g. of dioxime with 0.48 g. of pyruvic acid was accomplished by refluxing the components in 10 cc. of 50% acetic acid for 3 hours. After adding 0.22 g. of sodium acetate and diluting with water to saturation at about 60°, there was obtained upon cooling 0.21 g. (77%) of material, m.p. 126–128.5°.

Dehydroisoandrosterone acetate oxime. The oxime prepared in the usual way in dilute alcohol (2:1) in 92% yield, was microcrystalline, m.p. 162–163° (from dilute methanol or from benzene-ligroin).

Anal. Calc'd for $C_{21}H_{31}NO_2$: N, 4.05. Found: N, 4.20.

Dehydroisoandrosterone acetate was recovered in 75% yield upon refluxing 1.00 g. of the oxime for 4 hours with a solution of 0.78 g. of pyruvic acid and 0.38 g. of sodium acetate in a mixture of 5 cc. of acetic acid in 2 cc. of water. The solution became brown due to side reactions of the sodium pyruvate.

SUMMARY

A general procedure using pyruvic acid has been devised for the splitting of both keto-steroid semicarbazones and oximes, and recovery of the ketones. Its application to a number of mono and diketones is illustrated.

BLOOMFIELD, NEW JERSEY

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THE SYNTHESIS AND REACTIONS OF METHOXYINDOLE COMPOUNDS

JOHN B. BELL, JR.¹ AND H. G. LINDWALL

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A number of methoxy- and hydroxy-indole derivatives have been isolated by many investigators in connection with studies of the "toad poisons" and the Harmala alkaloids. Many of the simpler methoxyindole compounds and a few hydroxyindoles have been synthesized.

The synthetic approach has been continued in this research with the purpose of preparing and characterizing additional methoxyindoles and investigating their conversion to hydroxyindoles.

For the preparation of 2-carboxy-5-methoxyindole, the procedures of Blaikie and Perkin (1), and Wieland, Konz, and Mittasch (2), which are based on Reissert's work (3), are greatly inferior to that of Koelsch (4). Following essentially the procedure of the latter author we were able to convert *m*-cresol successively to a 2-nitroso-5-hydroxytoluene (nearly quantitatively); 2-nitro-5-hydroxytoluene (80%); 2-nitro-5-methoxytoluene (89%); 2-nitro-5-methoxyphenylpyruvic acid (57%), and 2-carboxy-5-methoxyindole (I), (60%). Thus the over-all yield from *m*-cresol is near 25%. The ethyl ester (II), of this compound can be obtained conveniently (in 52% yield) from the *p*-methoxyphenylhydrazone of ethyl pyruvate, which is readily available through the Japp-Klingemann reaction (5, 6), following the general procedure of Hughes, *et al.* (7). By saponification of the ester, the acid (I), may be obtained in excess of 90% yield, the over-all yield from *p*-anisidine being 47%.

Entry into the 7-methoxyindole series was accomplished solely by means of ring-closure of *o*-methoxyphenylhydrazones, prepared by the Japp-Klingemann reaction. The yield of 2-carboethoxy-7-methoxyindole (III) was 30% from *o*-anisidine, and the conversion to the acid (IV) proceeded in 85% yield.

In confirmation of the work of Späth and Brunner (8), the *o*-methoxy- and *p*-methoxy-phenylhydrazones of acetone gave no indole compounds which could be isolated using the normal Fischer procedure, *i.e.*, zinc chloride at 180°, with or without tetrahydronaphthalene as a solvent. Using the modified procedure of the above mentioned authors (ZnCl₂, 110°, under vacuum), approximately 20% yields (about one-half of that reported) of 2-methyl-5-methoxyindole (V), were obtained from the *p*-methoxyphenylhydrazone of acetone. Attempts at ring closure of the *o*- and *p*-methoxyphenylhydrazones of acetone using (a) ethyl alcohol saturated with HCl, or (b) ethyl alcohol containing 10% sulfuric acid, or (c) 50% glacial acetic acid-50% concentrated HCl, all failed.

The *p*-methoxyphenylhydrazone of diethylalyl acetate, on warming with

¹ We are indebted to the Squibb Institute for Medical Research for the Fellowship which supported this work.

² Present address: Jefferson Chemical Company, 30 Rockefeller Plaza, New York, N. Y.

10% sulfuric acid gave 1-(*p*-methoxyphenyl)-3-carboxypyrazolone-5 (VI), and not 2,3-dicarboethoxy-5-methoxyindole. This is not surprising, however, since this is the basis of a well known pyrazolone synthesis. When the *N*-methyl-*p*- and *o*-methoxyphenylhydrazones of diethyloxalyl acetate were treated with alcoholic HCl, the corresponding *N*-methyl-2,3-dicarboethoxy-5-methoxyindole and its 7-methoxy analog, respectively, were presumably formed. Unfortunately, it was not possible to crystallize these two compounds. On saponification with 30% KOH, each yielded an α -carboxylic acid, (VII and VIII), not the 2,3-dicarboxylic acid which might have been expected on the basis of Reif's (9) similar preparation of 1-methylindole-2,3-dicarboxylic acid. This

TABLE I
ANALYSES

COMPOUND NUMBER	FORMULA	CALCULATED			FOUND		
		C	H	N	C	H	N
VI	C ₁₁ H ₁₀ N ₂ O ₄	56.4	4.27	12.0	56.6	4.55	12.1
VIII	C ₁₁ H ₁₁ NO ₃	64.4	5.37	6.83	64.5	5.62	7.01
IX*	C ₁₆ H ₁₄ N ₂ O ₆	49.2	3.59	14.4	49.5	3.75	14.6
XIII	C ₁₃ H ₁₈ N ₂ O	71.6	8.28	12.8	71.8	8.55	13.0
XIV	C ₁₂ H ₁₆ N ₂ O	70.6	7.84	13.7	70.9	7.12	13.9
XV	C ₁₆ H ₂₀ N ₂ O ₃	65.2	7.25	10.2	65.5	7.27	9.96
XXVI	C ₁₆ H ₂₀ N ₂ O ₃	65.2	7.25	10.2	65.4	7.50	10.4
XXVII*	C ₂₀ H ₂₀ N ₆ O ₇	52.6	4.39	18.4	52.8	4.23	18.3
XXVIII	C ₁₃ H ₁₆ N ₂ O ₃	62.9	6.45	11.3	63.1	6.69	11.2
XXIX	C ₁₃ H ₁₆ N ₂ O ₃	62.9	6.45	11.3	63.0	6.71	11.4
XX	C ₁₆ H ₁₆ N ₂ O ₃	66.2	5.88	10.3	66.2	6.01	10.3
XXI	C ₁₆ H ₁₆ N ₂ O ₃	66.2	5.88	10.3	66.3	6.05	10.4
XXII	C ₁₄ H ₁₄ N ₂ O ₂	69.4	5.78	11.6	69.6	5.65	11.6
XXIII	C ₁₃ H ₁₃ NO ₅	59.3	4.94	5.32	59.4	5.01	5.36
XXIV	C ₁₃ H ₁₃ NO ₅	59.3	4.94	5.32	59.5	5.19	5.47
XXV	C ₁₂ H ₁₁ NO ₄	61.8	4.72	6.01	61.9	4.85	6.07
XXVII	C ₉ H ₉ NO	73.5	6.12	9.52	73.6	6.28	9.59
XXVIII	C ₉ H ₉ NO	73.5	6.12	9.52	73.8	6.44	9.49

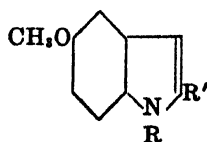
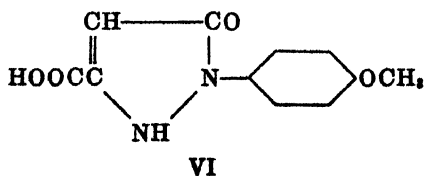
(* Picrate)

observation is similar to that of Diels and Reese (10), who obtained only indole- α -carboxylic acid upon saponifying the monoethyl ester of the 2,3-dicarboxylic acid.

1-Methyl-2-carboxy-5-methoxyindole (VII), has been decarboxylated to yield 1-methyl-5-methoxyindole (IX), an uncrystallizable liquid which forms a well defined picrate.

A number of 3-dimethylaminomethyl derivatives of 5-methoxy- and 7-methoxy-indole were prepared, with the possibility in mind that basic methoxyindole compounds might possess interesting pharmacological properties. The experimental procedures were based on those of previous investigators (11, 12, 13), who utilized the Mannich reaction for the introduction of the dimethylaminomethyl group.

The synthesis of 2-methyl-3-dimethylaminomethyl-5-methoxyindole (XIII), was quite unsatisfactory because of the very marked tendency of 2-methyl-5-

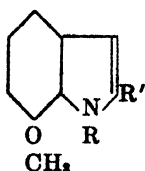


VII R = CH₃, R' = COOH

IX R = CH₃, R' = H

XX R = CH₂CH₂CN, R' = COOC₂H₅

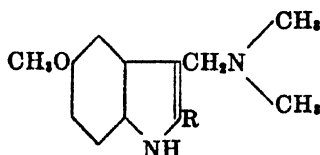
XXIII R = CH₂CH₂COOH, R' = COOH



VIII R = CH₃, R' = COOH

XXI R = CH₂CH₂CN, R' = COOC₂H₅

XXIV R = CH₂CH₂COOH, R' = COOH

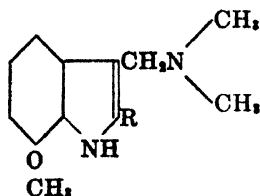


XII R = H

XIII R = CH₃

XV R = COOC₂H₅

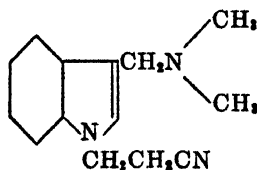
XVIII R = COOH



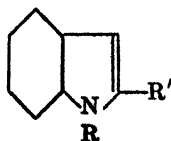
XIV R = H

XVI R = COOC₂H₅

XIX R = COOH

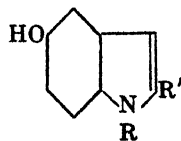


XVII



XXII R = CH₂CH₂CN, R' = COOC₂H₅

XXV R = CH₂CH₂COOH, R' = COOH



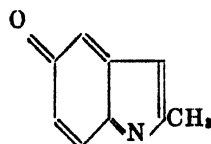
XXVI R = H, R' = H

XXVII R = H, R' = CH₃

XXVIII R = CH₃, R' = H



XXIX



XXX

methoxyindole (8) to give resinous condensation products in the presence of formaldehyde. Several early attempts gave no Mannich products whatsoever.

This would appear to be due to the combined activating influence of the 2-methyl group and the 5-methoxyl group on the indole nucleus. It should be noted that while Supniewski and Serafin-Gajewski (12) apparently had no difficulty in obtaining an 88% yield of 2-methylgramine, our experience and that of Brehm (11), was that the use of 2-methylindole derivatives invariably gave some resinous material and our yields of 2-methylgramine by the above authors' procedure (12) were near 50%. Although the 5-methoxy- and 7-methoxyindole have a greater tendency to form resinous products in the Mannich reaction than indole itself, they are less reactive in this respect than 2-methylindole, and fair yields are obtained without great difficulty. The combined influence of both the methyl and methoxyl groups, however, resulted in an 8% yield, at best, of 2-methyl-3-dimethylaminomethyl-5-methoxyindole (XIII). 2-Carboethoxy-5-methoxyindole and 2-carboethoxy-7-methoxyindole react smoothly in the Mannich reaction and these amino esters may, with care, be hydrolyzed to the amino acids.

It has also been possible to prepare N-cyanoethyl derivatives (XX and XXI) of 2-carboethoxy-5-methoxy- and 2-carboethoxy-7-methoxyindole, and from these to prepare the corresponding dibasic acids (XXIII and XXIV). The procedures employed in this connection were substantially those of Blume and Lindwall (14). 2-Carboethoxyindole was also cyanoethylated (XXII) and the product was then hydrolyzed to the dibasic acid (XXV) for purposes of comparison.

The cyanoethylation of gramine (13) yielded 1-cyanoethyl-3-dimethylaminomethylindole, (XVII), an uncrystallizable syrup, which could not be satisfactorily hydrolyzed to the amino acid in either acid or alkaline solution. Following the attempted hydrolysis, no product precipitated at pH 5-7. The same compound (XVII) was prepared by a Mannich reaction on 1-cyanoethylindole (14), the identity of the two compounds being established by comparison of the picrates.

Considerable difficulty was encountered in attempting to dealkylate representative methoxyindoles to yield the corresponding hydroxyindoles. Both AlCl_3 and N-methylaniline hydrobromide were used as dealkylating agents. It was found essential to operate in an atmosphere of nitrogen to protect the hydroxyindoles from oxidation. Even with this precaution, the yields were poor. In addition to 5-hydroxyindole (XXVI), the preparation of which (by a different and superior method) has been reported (15), 2-methyl-5-hydroxyindole (XXVII), 1-methyl-5-hydroxyindole (XXVIII), and 7-hydroxyindole (XXIX), have been prepared. Except for the 7-hydroxyindole there seems to be no doubt concerning the identities of the products. In the latter case, however, the compound was obtained in such low yield and questionable purity that only the demonstration of the presence of a phenolic hydroxyl group was possible.

There seems to be little choice between AlCl_3 and N-methylaniline hydrobromide as dealkylating agents as far as yield is concerned, although the isolation of the product is somewhat easier with latter.

Demethylation of 2-methyl-5-methoxyindole (V) in the presence of air by

both procedures gave a violet solid from which no hydroxy compound could be sublimed. The product was practically insoluble in water, soluble in alcohol and ether. The melting point was not sharp, but sintering began at about 200°. The nitrogen analysis was unacceptable for the expected 2-methyl-5-pseudoindolone (XXX).

EXPERIMENTAL

1-p-Methoxyphenyl-3-carboxypyrazolone-5 (VI). In a little dilute acetic acid, 1.38 g. (0.01 mole) of *p*-methoxyphenylhydrazine [m. p. 63–64°, 45% yield, (1)] was dissolved and mixed with 1.88 g. (0.01 mole) of diethylmalacetic acid (freed from 2.10 g. of its sodium enolate in alcohol with 1 ml. of acetic acid). Sodium acetate (1 g.) was then dissolved in the mixture. The oil which separated on standing resisted attempts to induce crystallization, and was dissolved in 20 ml., of 10% H₂SO₄ and warmed for a few minutes on the steam-bath. A solid separated which was crystallized from aqueous alcohol. There was obtained 2.04 g. (87.2%) of small, light tan crystals which melted with decomposition at 250–251°.

1-Methyl-2-carboxy-5-methoxyindole (VII). *Procedure A.* Seven and six-tenths grams (0.05 mole) of (unsym.) methyl-*p*-methoxyphenylhydrazine (prepared from *N*-methyl-*p*-anisidine) and 4.4 g. (0.05 mole) of freshly-distilled pyruvic acid were added to a mixture of 4 g. of glacial acetic acid in 20 ml. of water and warmed on the steam-bath for a few minutes. After the addition of 50 ml. of concentrated HCl, the mixture was again warmed on the steam-bath (fifteen minutes) and set in the ice-box overnight. The granular solid was crystallized from aqueous alcohol as a light tan powder melting at 215–216°, with decomposition [Kermack and Telrich (16) report 216°]; yield, 3.4 g. (33.2%).

The preparation of 1-methyl-2-carboxy-7-methoxyindole (VIII), melting with decomposition at 199–201°, from *N*-methyl-*o*-anisidine, was accomplished in the same manner but the yield was very poor [89 mg. from 12.5 g. of (unsym.) *N*-methyl-*o*-methoxyphenylhydrazine].

Procedure B. To 7.6 g. (0.05 mole) of (unsym.) methyl-*p*-methoxyphenylhydrazine dissolved in a little dilute acetic acid, was added 9.4 g. (0.05 mole) of diethylmalacetic acid (freed from 10.5 g. of its sodium enolate in alcohol with 4 ml. of acetic acid). Sodium acetate (5 g.) was dissolved in the mixture by warming. The oil which appeared on standing was separated and dissolved in 50 ml. of saturated alcoholic HCl. After warming for a few minutes on the steam-bath, the solution was cooled and diluted to twice its volume with water. The viscous syrup which separated could not be crystallized and was refluxed for one hour with 30% KOH. The cooled solution was made acid to Congo Red and, after chilling in the ice-box, the solid was recrystallized from aqueous alcohol. There was thus obtained 1.18 g. (11.5%) of a nearly white, granular powder melting at 215–216°, with decomposition. A mixed melting point with the known product from *Procedure A* gave no depression.

Application of the same procedure gave a poor yield (54 mg. from 12.5 g. of the hydrazine) of 1-methyl-2-carboxy-7-methoxyindole (VIII), m.p. 200–201°. A mixed melting point with the sample prepared by *Procedure A* showed no depression.

1-Methyl-5-methoxyindole (IX). Two and five-hundredths grams (0.01 mole) of 1-methyl-2-carboxy-5-methoxyindole was heated at 200° until the liquid melt no longer gave off CO₂. The 1.15 g. (71.5%) of straw colored liquid could not be induced to crystallize. A picrate melting at 97–98° was obtained, however, which crystallized from aqueous alcohol in red-orange needles.

Similarly, 5-methoxyindole (X), m.p. 54–55°, (65% yield) was prepared from (I), (Reference 1, 55°) and 7-methoxyindole (XI) m.p. picrate 155–156°, (53% yield) from IV (Reference 1, 156°).

3-Dimethylaminomethyl-5-methoxyindole. (5-Methoxygramine) (XII). To avoid loss of

the volatile amine, 5 g. (0.0367 mole) of 33% aqueous dimethylamine was added beneath the surface of 15 ml. of glacial acetic acid, then 3.5 g. (0.0238 mole) of 5-methoxyindole (X) was dissolved in the solution, which then was cooled to 0°; 3.2 g. (0.0394 mole) of 37% aqueous formaldehyde (which had previously been cooled to 0°) was added dropwise to the above solution in an ice-bath during one-half hour and it was allowed to stand at room temperature overnight. On dilution to four times its volume with water, the solution remained clear. When the reaction was not thoroughly cooled in the initial stage, a considerable amount of high-melting, resinous material separated on standing or on dilution; the solution then required filtration and the yield was poorer. The solution was made alkaline with NH_4OH until there was no further precipitation. The white solid was crystallized from very dilute acetone, dilute alcohol, or petroleum ether. There was obtained 3.5 g. (72%) of fine, white needles, melting at 127.5–128°.

[It should be noted that this compound has been prepared in 10% yield by Wieland and Hsing (17) who treated 5-methoxyindolemagnesium iodide with dimethylaminoacetonitrile.]

By the same procedure were prepared: 2-methyl-3-dimethylaminomethyl-5-methoxyindole (XIII), in 8% yield, m.p. 112–114°; 3-dimethylaminomethyl-7-methoxyindole (XIV), in 53% yield, m.p. 105–106°; 2-carboethoxy-3-dimethylaminomethyl-5-methoxyindole (XV), in 76% yield, m.p. 123.5–124.5°; 2-carboethoxy-3-dimethylaminomethyl-7-methoxyindole (XVI), in 62% yield, m.p. 110–112°; and 1-cyanoethyl-3-dimethylaminomethylindole (XVII), in 79% yield, m.p. of picrate 140–142°.

2-Carboxy-3-dimethylaminomethyl-5-methoxyindole XVIII. The hydrolysis of 1.38 g. (0.005 mole) of 2-carboethoxy-3-dimethylaminomethyl-5-methoxyindole (XV), was accomplished by refluxing for a few minutes with 30 ml. of 20% NaOH until all the ester dissolved. The reaction mixture was cooled immediately and made just acid to litmus with acetic acid. The slightly pinkish precipitate was crystallized from aqueous alcohol or alcohol and isopropyl ether. The white amorphous solid (440 mg., 35.5%) which was obtained melted with decomposition at 197–198°.

When the hydrolytic treatment was carried on for two hours no product resembling an amino acid could be isolated.

The corresponding 2-carboxy-3-dimethylaminomethyl-7-methoxyindole (XIX) was similarly obtained in 28% yield; m.p. 196–197°.

1-Cyanoethyl-2-carboethoxy-5-methoxyindole (XX). To a solution of 2.19 g. (0.01 mole) of 2-carboethoxy-5-methoxyindole in 30 ml. of dioxane, 0.6 g. (0.0113 mole) of acrylonitrile was added, followed by 0.3 ml. of trimethylbenzylammonium hydroxide solution (Triton B). The reaction mixture was warmed at 50°, for thirty minutes and permitted to stand at room temperature overnight. Water, containing a little acetic acid, was then added to increase the volume to 150 ml. The white needles which separated were crystallized from alcohol. A yield of 2.25 g. (82.7%) of fine white needles melting sharply at 112° was obtained.

The following were prepared in similar fashion: 1-cyanoethyl-2-carboethoxy-7-methoxyindole (XXI), m.p. 110–112°, in 72% yield; 1-cyanoethyl-2-carboethoxyindole (XXII), in 90% yield, m.p. 86–87°; and 1-cyanoethyl-3-dimethylaminomethylindole (XVII), in 90% yield, m.p. of picrate 140–142°. Compound XVII is identical with the product obtained by the Mannich reaction on N-cyanoethylindole.

The hydrolysis of XX, XXI, and XXII with 40% KOH gave β -(2-carboxy-5-methoxyindolyl-1)propionic acid (XXIII), in 88% yield, m.p. 208–209°; β -(2-carboxy-7-methoxyindolyl-1)propionic acid (XXIV), in 81% yield, m.p. 200–201°; and β -(2-carboxyindolyl-1)propionic acid (XXV), in 92% yield, m.p. 215°, respectively. Attempts to hydrolyze (XVII) to the amino acid were unsuccessful and destructive.

5-Hydroxyindole (XXVI). *Procedure A.* A solution of 1 g. (0.0068 mole) of 5-methoxyindole (X), in 10 ml. of dry benzene with 2.5 g. (0.0235 mole) of anhydrous AlCl_3 was refluxed gently for ten hours in an atmosphere of nitrogen. The reaction mixture was decomposed with 20 ml. of ice-water and the aqueous solution was extracted with two additional 10-ml. portions of warm benzene. The combined benzene portions were evaporated to dryness under nitrogen. The residue (390 mg.) was warmed with petroleum ether, filtered and con-

centrated to a small volume. The impure tan solid which separated melted at 103–107°, (180 mg., 20%) and was most successfully purified by sublimation under vacuum, which yielded 55 mg. (6.1%) of white solid melting at 107–108°. Bergel and Morrison (15) reported 107–109°.

Using the above procedure, 2-methyl-5-methoxyindole (8) (V), (m.p. 85–86°) gave 2-methyl-5-hydroxyindole (XXVII), m.p. 134–136°, in 14% yield.

Procedure B. A mixture of 1 g. (0.0068 mole) of 5-methoxyindole with 3 g. (0.016 mole) of N-methylaniline hydrobromide was melted in an oil-bath for one-half hour at 220°, in an atmosphere of nitrogen. On cooling, trituration with 20 ml. of water and addition of a few drops of HCl, a brown solid separated, which when dried in a vacuum and sublimed in a vacuum gave 146 mg. (16%) of white solid melting at 107–108°. This product was identical (mixed melting point) with the product from *Procedure A*.

In a similar manner XXVII was prepared in 21% yield. 1-Methyl-5-methoxyindole (IX) gave a 15% yield of 1-methyl-5-hydroxyindole (XXVIII), m.p. 42–45°. An attempt to convert 7-methoxyindole (XI) to 7-hydroxyindole (XXIX) by this procedure gave a 3% yield of a light yellow viscous liquid, which gave a low nitrogen analysis.

A dilute solution of FeCl₃ gave a deep purple color with XXVI, XXVII, and XXIX, while XXVIII gave a red color which slowly became purple. All gave a pink color with Ehrlich's reagent.

SUMMARY

1. A number of 5-methoxy- and 7-methoxy-indole derivatives have been prepared.

2. Methoxyindoles have been found to undergo the Mannich reaction and cyanoethylation.

3. Hydrolysis of 1-methyl-2,3-dicarboethoxy-5-methoxyindole and the 7-methoxy analog yielded only the α -carboxylic acids.

4. Demethylation of a few 5-methoxyindoles to 5-hydroxyindoles has been accomplished.

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THE ACTION OF NITROUS ACID UPON CREATININE AND SOME OF ITS DERIVATIVES

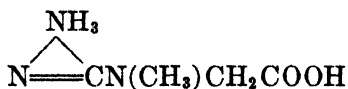
ISIDOR GREENWALD AND IRVING LEVY¹

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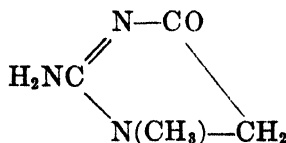
The work discussed in the present paper is an attempt to determine the reactivity of nitrous acid with creatinine and several of its derivatives and to consider the significance of the results for the formulation of the constitution of these substances.

Wilson (1) and Plimmer (2) found that creatine, for which the usual formula indicates an amino group, did not react with nitrous acid or did so only slowly and incompletely; whereas creatinine, for which the usual formula does not indicate an amino group, reacted quite rapidly.

Plimmer (2) added the observation that, in the presence of hydrochloric acid, creatine did liberate gas, whereas the yield from creatinine was diminished. He, therefore, proposed the alternative formulas I and II for creatine and creatinine, respectively, as expressing the state of the substance in aqueous solution and suggested that the usual formulas express the structures existing in solutions containing hydrochloric acid.



I



II

We confirmed Plimmer's report as to the effect of hydrochloric acid upon the reactivity of creatinine and nitrous acid. We mixed the creatinine with hydrochloric acid before adding it to the reaction mixture and used such small quantities of hydrochloric acid that they could not have affected the *pH* of the reaction mixture appreciably. We are, therefore, of the opinion that there are two tautomeric forms of creatinine, one of which is stable at low *pH* and does not react with nitrous acid.

However, if Plimmer's formulation were correct, methylcreatinine and N-benzylcreatinine should not react with nitrous acid or do so but slowly. Actually, they do (Table I, entries 6 to 12, 14 and 15), and rapidly and without apparent interference by small amounts of hydrochloric acid.

Since the *pH* of a solution of creatinine picrate is about 3.9 (glass electrode) and since that of the reaction mixture of acetic acid and nitrous acid cannot be far removed from this, it would appear that about ten per cent of the creatinine exists in the non-reactive form at this *pH* (entry 4). Moreover, since some re-conversion to the reactive form may be expected to have occurred in the reaction

¹ Present address: De Witt Clinton High School, New York.

TABLE I

LIBERATION OF NITROGEN BY ACETIC ACID AND SODIUM NITRITE FROM CREATININE AND ITS DERIVATIVES

(The figures represent percentages of calculated yield of one atom per molecule. Only one value is reported if duplicate analyses yielded concordant results.)

NO.	SUBSTANCE	SOLVENT	NITROGEN LIBERATED IN, MINUTES		
			3	15	30
			Molar percentage		
1	Creatine	H ₂ O	0.4	7.2	7.5
2	Creatinine	H ₂ O	22-45	88	101
3	Creatinine HCl	0.04 <i>M</i> HCl ^a	16-23	46	51
4	Creatinine picrate	H ₂ O	21	80	90
5	Creatinine	0.1 <i>M</i> NaOH ^b	19-28	83-91	97
6	Methylcreatinine HI	H ₂ O	33	88	99
7	Methylcreatinine HCl ^c	H ₂ O	50	96	100
8	Methylcreatinine picrate	H ₂ O	39	87	107
9	Methylcreatinine picrate	0.04 <i>M</i> HCl ^a	45		
10	Methylcreatinine HCl ^c	0.9 <i>M</i> HCl ^a		90	
11	Methylcreatinine HI	0.04 <i>M</i> HCl ^a	41		
12	Methylcreatinine H ₂ SO ₄	H ₂ O	51	94	94
13	Methylcreatinine HI	0.04 <i>M</i> NaOH ^{a, b}			14
14	N-benzylcreatinine	H ₂ O		90	103
15	N-benzylcreatinine HCl	H ₂ O	62	92	111
16	Creatinine oxime	0.04 <i>M</i> NaOH ^a	81-97	104	
17	Creatinine oxime	0.44 <i>M</i> NaOH ^a	56		102
18	Methylhydantoin oxime	0.065 <i>M</i> NaOH ^a			10-30
19	Dimethylhydantoin oxime	0.068 <i>M</i> NaOH ^a		85	95
20	Methylhydantoin	H ₂ O			2
21	Acetylcreatinine	H ₂ O	13	24	32
22	Benzoylcreatinine ^e	0.96 <i>M</i> NaOH ^a	4	10	10 ^f
23	Benzalcreatinine, 2 HCl	H ₂ O	36	108	136
24	Benzalcreatinine	10% Acetic acid	24	83	99
25	5-Benzylcreatinine	H ₂ O		90	103
26	Dimethylcreatinine HCl ^c	H ₂ O		52	58
27	Dimethylcreatinine HI	H ₂ O	22-36	34-45	46-53
28	Dimethylcreatinine HI	0.07 <i>M</i> HCl ^a		34	
29	Dimethylcreatinine HI	0.07 <i>M</i> HCl ^{a, d}		41	
30	Glycocyanine	H ₂ O	5	13	26
31	Glycocyanidine HCl	H ₂ O	37	77	90
32	3-Methylglycocyanidine picrate	H ₂ O	38	66	70
33	Dicreatinine picrate HBr	H ₂ O	47-68	110	125

^a The concentration of hydrochloric acid and of sodium hydroxide are those calculated as remaining after displacement of picric acid or of hydroiodic acid from the salts or of one proton from benzoylcreatinine or any of the oximes; or the addition of one proton to creatinine.

^b The mixtures were prepared one hour before use.

^c Prepared from the hydriodide by treatment with freshly precipitated silver chloride.

^d After standing eight days.

^e In a previous paper (10) it had been assumed, because of the different crystal forms, that the benzoylcreatinine made from creatinine and benzoyl chloride (plates) was an isomer of that obtained by heating creatinine with benzoic anhydride (needles). Ing (7) claimed that the supposed isomer was a mixture of benzoylcreatinine and tribenzoyl creatinine. Our preparations did not contain tribenzoylcreatinine. However, upon recrystallization from alcohol, particularly in the presence of a few needles, the plates changed to needles. Determinations of the solubility of the two materials, separately or together indicated that they were different crystal forms of the same substance.

^f The low yield of gas when treated with nitrous acid was probably due to precipitation of benzoylcreatinine in the reaction chamber.

vessel in the experiments summarized in entry 3, it would appear that more than half of the creatinine at pH 1.4 was in this non-reactive form. At the lower pH prevailing in Plimmer's mixtures containing 5, 6, 7, and 8 ml. of concentrated hydrochloric acid, still more of the creatinine would have been in this inactive form and the approximately 0.5 atom of nitrogen liberated might well have been formed during the first few minutes (as Plimmer recognized), before all the acid had been added. Whatever the change may be, it does not seem to occur if the two hydrogens in position 5 are replaced by a benzal group (entries 23 and 24).

The removal of one atom of nitrogen from creatinine should result in the formation of methylhydantoin. Indeed, Schmidt (3), thirteen years before Plimmer, had shown that creatinine in approximately 23% nitric acid, to which an excess of sodium nitrite was added, deposited a mixture of a small quantity of creatinine oxime and a large quantity of methylhydantoin oxime.

Experiment showed that gas was liberated from creatinine oxime more rapidly than from creatinine, indicating that the reaction might be creatinine oxime \rightarrow methylhydantoin oxime (entries 16 and 17). However, methylhydantoin oxime, dissolved in NaOH, in order to get it into the apparatus, also liberated gas (entry 18). Dimethylhydantoin oxime yielded even more (entry 19). Apparently, the addition of alkali to either of these oximes produces a change in configuration which is not readily reversed by the acetic acid in the reaction mixture. The postulated isomers are acted upon by nitrous acid, with the liberation of gas. Methylhydantoin, itself, dissolved in water, gave only traces of gas (entry 20).

It seems, therefore, quite likely that the reaction is creatinine \rightarrow methylhydantoin in the dilute solution employed in the determination, and to creatinine oxime and then to methylhydantoin oxime in the more concentrated mixtures. The methylhydantoin oxime isolated could scarcely have been formed from methylhydantoin because the latter, when added to a mixture of sodium nitrite and acetic acid, yielded no oxime but was recovered unchanged upon extraction with chloroform.

When the same preparative technic was applied to methylcreatinine hydrochloride, no methylcreatinine oxime was obtained. Instead, 60% of the material employed was accounted for as dimethylhydantoin oxime, identified by analysis and by conversion to dimethylparabanic acid. However, Zeile and Meyer (4) have obtained and described the hydrochloride of methylcreatinine oxime. This was formed in the presence of an excess of hydrochloric acid; when an excess of sodium nitrite was present, the product was dimethylhydantoin oxime.

The fact that methylcreatinine reacted so readily indicated that the second methyl group is in position 3 and not in 2. Zeile and Meyer (4), came to a similar conclusion in spite of the opposite view held by Nicolet and Campbell (5) and by Cornthwaite (6).

Ing (7) has presented evidence for regarding acetylcreatinine and benzoylcreatinine as being substituted in position 2. Since neither of these (entries 21, 22) reacted rapidly and since, in large-scale experiments, benzoylcreatinine yielded only benzoylcreatinine oxime, Ing's views would seem to have been

confirmed. Such liberation of nitrogen as did occur might be considered as having taken place after hydrolysis.

However, this interpretation is contradicted by the fact that dimethylcreatinine (entries 26 to 29) reacted to a greater extent than did acetylcreatinine. In dimethylcreatinine, all the nitrogen atoms are methylated and there can be no question of hydrolysis.

Other compounds related to creatinine were also tested with nitrous acid (entries 30-33). Glycoyamine reacted to a greater extent than did creatine; glycoyamidine hydrochloride almost as much as did creatinine; methylglycoyamidine picrate to a greater extent than did creatinine picrate. The compound of two molecules of creatinine and one of picric acid, in which the creatinine is present in a form that does not give Jaffe's reaction (8) yielded more gas than did the equivalent amount of creatinine, added as the free base, the picrate or the hydrochloride.

In contrast to the apparent stability of creatinine to 0.1 *M* sodium hydroxide for one hour, is the great lability of methylcreatinine to an even lower concentration (entry 13). Colorimetric analysis, using Jaffe's reaction and creatinine as a standard, of some of the same mixture as was used for the gasometric determinations, showed it to contain 23% of the expected amount of methylcreatinine. However, at the end of an hour, when the diluted alkaline picrate solutions were again compared with one another, the readings indicated the presence of 37% of the calculated amount of methylcreatinine. In another experiment, in which the undiluted mixtures of creatinine, or methylcreatinine, picric acid and sodium hydroxide were allowed to stand an hour before dilution and comparison, the readings indicated the presence of 79% of the calculated amount.

Apparently, the ring in methylcreatinine is more readily opened by hydroxyl ions than is that in creatinine but, as enolization takes place in more concentrated alkali and as complex formation with picrate occurs, it tends to close again.

The same ready opening of the ring in methylcreatinine was observed by Zeile and Meyer (4) when they attempted to prepare methylcreatinine by Cornthwaite's method. We succeeded once in the preparation by Cornthwaite's method but, thereafter, always encountered opening of the ring, whether we used that method or Korndorfer's (9), which had previously given good results. Finally a satisfactory product was obtained by treating methylcreatinine sulfate with ammonia, as described in the experimental part.

Attempts were made to isolate the products of the reaction between nitrous acid and creatinine and some of its derivatives. Under the conditions chosen, which except for time and the concentration of the "creatinine", were similar to those obtaining in the Van Slyke analysis, the following substances were isolated and identified: from creatinine, the oximes of creatinine and methylhydantoin; from methylcreatinine, dimethylhydantoin oxime; from *N*-benzylcreatinine, benzylmethylhydantoin oxime; from benzoylcreatinine, benzoylcreatinine oxime.

Dimethylcreatinine yielded a mixture of substances, which were not separated satisfactorily. In one experiment, what appeared to be two different substances, of widely different melting points, were obtained. The empirical constitution

of both was that of dimethylhydantoin oxime but neither yielded dimethylparabanic acid upon hydrolysis. In another experiment, the bulk of the product had a melting point which was different from that of either of the other two materials or from that of pure dimethylhydantoin oxime but it yielded dimethylparabanic acid upon hydrolysis.

We wish to thank Mr. D. Rigakos for the determinations of carbon, hydrogen, and nitrogen.

EXPERIMENTAL

Except as mentioned below, all the derivatives of creatinine were prepared by the methods used in previous work (10).

Benzalcreatinine and its dihydrochloride were prepared by the method of Nicolet and Campbell (5).

Methylcreatinine. To 18 g. of methylcreatinine hydrogen sulfate (6), dissolved in 200 ml. of hot absolute alcohol, 12 ml. of concentrated NH_4OH was added with constant shaking. The mixture was cooled in ice, filtered, and the precipitate was washed with absolute alcohol. The filtrate and washings were evaporated, under diminished pressure, with a bath temperature of 35° , to about 15 ml. Some crystals had separated. Fourteen milliliters of anhydrous ether was added and, after a few hours, the mixture was filtered and the precipitate was dried over H_2SO_4 and then over P_2O_5 . The yield was practically the theoretical. The crystals melted at 70° , and recrystallization either from alcohol (9) or from acetone (6) raised the m.p. only to about 73° , not the previously reported 80° . However, even the crude product could be used for the preparation of dimethylcreatinine hydriodide with perfectly satisfactory results.

Creatinine oxime and methylhydantoin oxime. A suspension of 5 g. of creatinine in 10 ml. of water was added in small quantities with constant stirring to a mixture of 8.4 g. of sodium nitrite, 25 ml. of H_2O and 7 ml. of glacial acetic acid. After standing at 10° for two days, the precipitate was filtered off, washed, and dried over KOH . It weighed 4.4 g. Extraction with hot alcohol yielded 2.3 g. of methylhydantoin oxime (m.p. 196° ; diacetyl deriv., m.p. 187°). The material insoluble in alcohol was dissolved in 0.25 *M* NaOH , reprecipitated with acetic acid, washed and dried. It weighed 1.5 g., decomposed above 252° and yielded a diacetyl derivative of m.p. 208° .

Dimethylhydantoin oxime. Similar experiments in which methylcreatinine hydrochloride or hydrogen sulfate were used yielded no material insoluble in alcohol but only an alcohol-soluble material, of m.p. 236° .

Anal. Calc'd for $\text{C}_8\text{H}_{11}\text{N}_3\text{O}_3$: C, 38.19; H, 4.49; N, 26.76.

Found: C, 38.66; H, 4.2; N, 25.90.

Upon hydrolysis with HCl (4) it yielded dimethylparabanic acid; crystals, from alcohol, of m.p. $150\text{--}151^\circ$.

Oxime of 1-methyl-3-benzylhydantoin. *N*-benzylcreatinine hydrochloride yielded only a small amount of material that was insoluble in alcohol. This dissolved in NaOH and was reprecipitated by acetic acid. It darkened above 262° but did not melt even at 355° . The alcohol-soluble material was crystallized twice from 50% alcohol, and then melted at 183° .

Anal. Calc'd for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_3$: C, 56.64; H, 4.75; N, 18.01.

Found: C, 56.79; H, 4.34; N, 17.97.

Oximes from dimethylcreatinine. A solution of dimethylcreatinine hydriodide was treated with freshly precipitated silver chloride. The mixture was filtered and the filtrate and washings were evaporated, under diminished pressure, to small volume. Upon treatment with sodium nitrite and acetic acid, a crystalline material was obtained. This was fractionated into two portions, one less soluble in alcohol (A) of m.p. 206° and one more soluble (B) of m.p. $140\text{--}142^\circ$.

(A) Found: C, 37.98; H, 4.43; N, 26.25.

(B) Found: C, 38.28; H, 4.54; N, 26.48.

These figures agree very well with those calculated for dimethylhydantoin oxime. Some of each fraction was mixed with pure dimethylhydantoin oxime. The m.p. of the mixture with A was 208–210°; of that of the mixture with B was 185–195°. Neither A nor B yielded dimethylparabanic acid upon treatment with HCl.

In another experiment, the bulk of the material melted above 175°. This was not analyzed but, upon hydrolysis, yielded typical crystals of dimethylparabanic acid, m.p. 150°, unchanged by mixture with material obtained from pure dimethylhydantoin oxime.

Benzoylcreatinine oxime. Benzoylcreatinine (1.76 g.) was ground with 30 ml. of 0.04 *M* sodium hydroxide. There were then added 10 ml. of 30% sodium nitrite and 50 ml. of 20% acetic acid. After standing 24 hours, the mixture was filtered and the precipitate was washed, air-dried, and extracted with benzene to remove a small quantity of unchanged benzoylcreatinine. The residue was dissolved in 0.1 *M* sodium hydroxide and reprecipitated with acetic acid. After being filtered, washed, and dried, it melted at 129–130°; yield 1.79 g., or 90% of that calculated. Four-tenths gram was dissolved in 5 ml. of warm concentrated hydrochloric acid and the solution was then placed in a vacuum desiccator containing potassium hydroxide. The dry residue was extracted with ether. The ether was evaporated and the residue was recrystallized from water. It melted at 120° and 0.0786 g. required 0.61 ml. of 0.1014 *M* sodium hydroxide for a titration to pH 8.5; calculated for benzoic acid, 0.636 ml. The aqueous mother liquids from the benzoic acid were evaporated to dryness. The residue, after crystallization from alcohol, melted at 152–153°, unchanged upon mixing with pure methylparabanic acid. The material insoluble in ether weighed 0.11 g., melted at 147° and contained 48.4% chlorine and 19.0% nitrogen. It was, apparently, hydroxylamine hydrochloride, containing 51% chlorine and 20% nitrogen, contaminated with some material of lower chlorine and nitrogen content.

SUMMARY

The reaction between nitrous acid and creatinine and several of its derivatives was studied. The results indicate the existence of a tautomer of creatinine that is stable at low *pH* and that does not react with nitrous acid. This type of tautomerism does not occur with methylcreatinine, which reacts readily to form dimethylhydantoin oxime. Dimethylcreatinine is less reactive than methylcreatinine but also forms a compound of the composition of dimethylhydantoin oxime.

A method for the preparation of free methylcreatinine is described.

Attention is directed to the ready opening of the ring in methylcreatinine.

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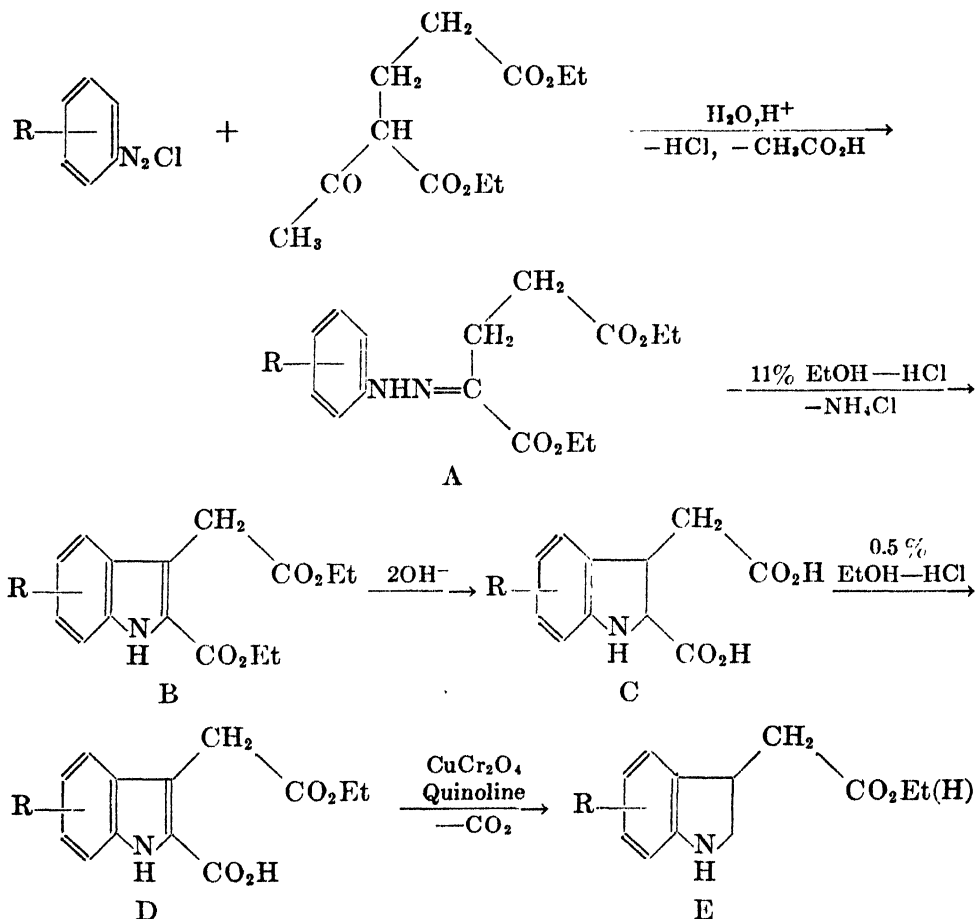
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THE SYNTHESIS OF CERTAIN SUBSTITUTED
INDOLEACETIC ACIDS¹

STEPHEN P. FINDLAY AND GREGG DOUGHERTY

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In connection with a study of the relation of structure to the plant growth regulating properties of organic compounds, several 3-indoleacetic acids substituted in the benzene ring have been prepared. The synthesis involved the application of the Japp-Klingemann reaction (1) for the formation of phenylhydrazones, the Fischer synthesis (2) for ring closure followed by hydrolysis of a diester, reesterification to a half ester, and decarboxylation.

R = OCH_3 or C_4H_4

¹ Abstracted from a dissertation submitted by Stephen P. Findlay to the Department of Chemistry, Princeton University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Through C, the scheme is essentially that employed by Manske and Robinson (3) to prepare β -(3-indolyl) propionic acid.

King and L'Ecuyer (4) and Tanaka (5) applied it to the preparation of unsubstituted indoleacetic acid, but the sequence in its entirety has not heretofore been applied to the rather sensitive and unstable nuclear substituted indole acids.

The compounds prepared were 5-, 6-, and 7-methoxyindoleacetic acids and 1- and 3-naphthazoleacetic acids. The 5-methoxy compound has been prepared previously by another method (6); the others do not appear in the literature and apparently have not been made before. In addition, the intermediate hydrazones necessary for the synthesis of 5,6-dimethoxyindoleacetic and three of the isomeric monochloroindoleacetic acids were obtained by the Japp-Klingemann reaction but some or all of the subsequent steps leading to the pure acids could not be carried out successfully.

Formation of the hydrazones. Although the formation of the hydrazones can take place under either acid or basic conditions, the monomethoxy compounds were obtained in higher yield in alkaline medium. The *o*-methoxy and ortho, meta, and para chlorophenylhydrazones of diethyl α -ketoglutarate were isolated as such; the others were used in the crude state for the subsequent cyclization process. It is worth noting that the hydrazones isolated were obtained initially as red or orange-red oils which could not be induced to crystallize. Treatment of the oils, however, with ethanolic hydrogen chloride produced the crystalline hydrazones accompanied by a distinct change of color. Furthermore, these crystals would not promote crystallization of the oils. This suggests that the initial step in the reaction was the formation of a diazo compound which was decomposed with rearrangement by strong acids.

The cyclization reaction. The literature contains accounts (7, 8) of the cyclization by alcoholic mineral acids of phenylhydrazones identical with or similar to some of those described here. In the cases of the methoxyphenylhydrazones the disposition has been to use 15–20% ethanolic HCl. It has been found in the present work that much better yields are obtained by the use of 8–11% acid. This concentration of acid was also sufficient to cyclize the naphthylhydrazones. On the other hand the conditions for cyclization of the chlorophenylhydrazones are considerably more vigorous than for most unsubstituted compounds. Ethanolic HCl alone or with zinc chloride had little effect. With *n*-butanolic mineral acids, cyclization occurred as indicated by the formation of ammonium salts, but no definite compounds could be isolated from the organic residue.

Miscellaneous observations. The indole diesters, B, with the exception of the 7-methoxy compound, were readily convertible to the corresponding diacid salts by refluxing with alcoholic alkali. The 7-methoxy compound was found to be unstable under the ordinary methods of saponification and was degraded largely to tarry material. However, the action of a dilute solution of potassium hydroxide in 99% ethanol at room temperature gave satisfactory results. The indole diacids were obtained as white microcrystalline substances which melted with decomposition above 200°.

The various indoleacetic acids were prepared by partial esterification of the corresponding 2-carboxy-3-indoleacetic acids, decarboxylation of the half ester so

obtained, and saponification. The decarboxylations proceeded rather smoothly in all cases but one, although, owing no doubt to the essential sensitivity of these compounds, the over-all yields were poor. The manner of preparation of the half esters, D, appears to exclude the possibility of obtaining 2-carboxyskatole as a final product. Indeed the 5- and 7-methoxy derivatives of 2-carboxyskatole are known and melt considerably higher than the isomeric indoleacetic acids. Where such isomers were also unknown, Ehrlich's reagent has been relied upon as a confirmatory diagnostic. It has been observed that when the 2-carboxyl group is removed, Ehrlich's reagent produces a color of heightened intensity (9).

EXPERIMENTAL

Copper-chromium oxide catalyst. This was prepared according to the directions of Connor, Folkers, and Adkins for the 39KAF modification using one-third quantities (10).

Ethyl β -bromopropionate. β -Bromopropionic acid was converted to the ethyl ester, b.p. 98°/49 mm., in 90% yield according to the directions of Kendall and McKenzie (11).

Ethyl α -acetoglutarate. Two moles (260 g.) of dry ethyl acetoacetate was added slowly to an ice-cold solution of sodium ethoxide made by dissolving one mole (23.0 g.) of sodium in 400 ml. of 99% ethanol. The mixture was warmed to 56–60° and 145 ml. (1.01 mole) of ethyl β -bromopropionate was added over a period of one and a half hours. The mixture was allowed to stand at room temperature for two days, refluxed for two hours on the steam-bath, cooled, and diluted with 200 ml. of dry ether. When most of the sodium bromide appeared to have separated it was removed and the ethanol, ether, and excess ethyl acetoacetate were fractionally distilled off and the product collected: 184 g. (80%), b.p. 140–142°/7 mm. The use of excess ethyl acetoacetate is a variation of procedures in the literature and had the effect of appreciably increasing the yield (12).

2-Carboxy-5-methoxy-3-indoleacetic acid. (a) *From the crude p-methoxyphenylhydrazone of diethyl α -ketoglutarate prepared in alkaline medium.* A diazonium chloride solution prepared from 2.5 g. of *p*-anisidine in 15 ml. of water was added to an ice-cold solution of 4.6 g. of diethyl α -acetoglutarate and 1.8 g. of sodium hydroxide in 33 ml. of 90% ethanol. The reaction mixture turned bright orange immediately, gradually deepened to blood red, and finally a red oil separated. After making slightly acid, the oil was extracted with ether and the extract washed with aqueous sodium chloride solution. The extract, dried several days over sodium sulfate, gave on removing the solvent a reddish brown oil which did not crystallize on standing.

Cyclization. The oil was taken up in 15 ml. of 11% ethanolic hydrogen chloride and refluxed gently thirty minutes on the steam-bath. Precipitation of ammonium chloride soon became noticeable. The mixture was cooled, poured into 50 ml. of water, and extracted with ether. After washing the extract with water and aqueous sodium bicarbonate, it was dried and the solvent removed.

Saponification. The residual oil was heated gently on the steam-bath for fifteen minutes with 1.6 g. of sodium hydroxide dissolved in 8 ml. of ethanol and 2 ml. of water. After dilution, the diacid was precipitated by acidification with 5 *N* hydrochloric acid: 2.9 g. (58%) of brown, granular material, m.p. 235–240°. One recrystallization from glacial acetic acid afforded 2.4 g. (48%) of tan microcrystalline material, m.p. 253.5–254.5° (decomp.): reported, 265° (decomp.) (7). This compound and related indole diacids underwent appreciable decomposition at elevated temperatures so that the melting point of a given sample depended in some measure upon the rate at which the compound was brought to the observed point of fusion.

(b) *From the p-methoxyphenylhydrazone prepared in acidic medium.* After preparing *p*-methoxybenzenediazonium chloride as above described, it was poured with shaking into a cold solution of 3.7 g. (0.045 mole) of sodium acetate in 33 ml. of 90% ethanol to which 4.6 g.

of the keto ester had been added just previously. The resulting clear brown solution soon became turbid and precipitated a dark brown oil, which was taken up in ether and washed with water, aqueous sodium bicarbonate, and aqueous sodium chloride. The brown oil obtained from the ether extract was cyclized and saponified as in the above case. The crude diacid, 1.9 g. (38%), m.p. 239–240°, on recrystallization from glacial acetic acid gave 1.6 g. (33%) of tan crystals, m.p. 257° (decomp.).

Attempted partial decarboxylation of 2-carboxy-5-methoxy-3-indoleacetic acid. This diacid could not be partially decarboxylated according to the procedure of King and L'Ecuyer, who removed the 2-carboxyl group of 2-carboxy-3-indoleacetic acid by heating the latter compound with copper powder in quinoline (4).

Ethyl 2-carboxy-5-methoxy-3-indoleacetate. A mixture of 25 ml. of 0.5% ethanolic hydrogen chloride and 2.5 g. of the diacid was refluxed two hours and most of the solvent removed under diminished pressure. The cold residue furnished 2.0 g. of crude product. Two crystallizations from aqueous ethanol provided pure material, m.p. 201.5–203.5° (decomp.).

Anal. Calc'd for $C_{14}H_{15}NO_5$: C, 60.61; H, 5.45.

Found: C, 60.56; H, 5.39.

This half ester was soluble in aqueous sodium bicarbonate, benzene, ether, and ethanol. With Ehrlich's reagent was obtained only a faint reaction.

5-Methoxy-3-indoleacetic acid. (a) *Decarboxylation of the half ester.* The half ester was conveniently decomposed by Tanaka's procedure. To 5 ml. of quinoline was added an intimate mixture of 0.50 g. of half ester and 90 mg. of catalyst 39KAF. This was heated in a Wood's metal-bath at 195–205°, the theoretical quantity of carbon dioxide being collected in a gas burette over toluene. The reaction mixture was digested with 50 ml. of ether, the catalyst filtered off, and the filtrate extracted with dilute hydrochloric acid and washed. After drying, the ether was removed, the residue saponified with an excess of ethanolic sodium hydroxide, and the product separating on acidification recrystallized twice from hot water: 0.10 g. of pure 5-methoxy-3-indoleacetic acid, m.p. 146° (decomp.): reported, 146–147° (decomp.) (6). It reacted with Ehrlich's reagent to give a violet color on warming and this was converted to a deep wine red by the addition of a trace of solid sodium nitrite.

Ethyl 2-carboethoxy-5-methoxy-3-indoleacetate. This was obtained from the cyclization residue which above was saponified without preliminary isolation of the diester. This compound, soluble in most of the common organic solvents, could be crystallized from benzene-ligroin or aqueous ethanol. The pure material crystallized from the latter solvent in pale yellow needles, m.p. 110–110.5°. It responded very faintly to Ehrlich's test.

Anal. Calc'd for $C_{16}H_{19}NO_5$: N, 4.60. Found: N, 4.79.

o-Methoxyphenylhydrazones of diethyl α -ketoglutarate. Although this compound may be prepared in both alkaline and acidic media, the yield in alkaline solution was found to be superior. Prepared from *o*-anisidine using the same quantities and procedure as for the *p*-methoxy isomer, it could be isolated or cyclized in the crude condition. In the former case, unlike the phenylhydrazone itself, the residual oil was observed to crystallize neither on long standing nor on seeding. However, treating with 10 ml. of cold 11% ethanolic hydrogen chloride converted the material, presumably a diazo compound, into the phenylhydrazone, which could be crystallized from methanol or aqueous ethanol. The pure material consisted of yellow aciculae, m.p. 81.5–82.5°.

Anal. Calc'd for $C_{18}H_{22}N_2O_5$: C, 59.61; H, 6.88; N, 8.69.

Found: C, 59.90, 59.63; H, 7.31, 6.95; N, 8.51, 8.52.

Saponification gave an acid which, after two recrystallizations from methanol, appeared as fine, brownish orange needles, m.p. 171.5° (decomp.): reported, 168° (decomp.) (7).

Ethyl 2-carboethoxy-7-methoxy-3-indoleacetate. Usually the *o*-methoxyphenylhydrazone was cyclized in the same manner as the *p*-methoxy isomer without prior purification. The cyclization product was always contaminated by large quantities of dark, viscous oil, the amounts of which increased with increasing strength of the alcoholic hydrogen chloride. It was found that the crude cyclization product, obtained in the same manner as the 5-methoxy analog from 0.02 mole of *o*-anisidine, could not be successfully saponified without

preliminary purification. In a typical experiment the crystalline material was freed of the oily impurities by drying on porous earthenware. Crystallization from ethanol gave 1.2 g. (20%) of material, m.p. 109.5–112.5°. Repeated recrystallization of the diester gave brown needles of pure material, m.p. 116°: reported, gray needles, m.p. 106° (7).

Anal. Calc'd for $C_{16}H_{19}NO_5$: N, 4.60. Found: N, 4.59.

Saponification to 2-carboxy-7-methoxy-3-indoleacetic acid. Considerable difficulty was encountered in transforming the 7-indole diester satisfactorily into the diacid. Heating a sample with a two-fold excess of 0.1 *N* ethanolic sodium hydroxide on the steam-bath for ten minutes caused extensive degradation, the amount of recoverable diacid being trivial. Results with longer heating time at 50° were no more encouraging. Partial saponification with 20% ethanolic potassium hydroxide at 25° or at higher temperatures gave starting material and a small amount of tan, crystalline material, m.p. 183°, which was not identified.

Finally, satisfactory results were obtained with potassium hydroxide dissolved in 99% ethanol. The pure ester (2.1 g.) was dissolved in 15 ml. of a 0.89 *N* solution of potassium hydroxide in 99% ethanol. After 48 hours in a stoppered flask at room temperature the voluminous, granular, pale yellow precipitate which had accumulated was collected and washed with 99% ethanol. The dried residue, aggregating 1.9 g., was dissolved in 10 ml. of warm water and, on acidifying the clear solution with 1 *N* hydrochloric acid, a yellow precipitate of 2-carboxy-7-methoxy-3-indoleacetic acid was obtained: 1.3 g., m.p. 213–214°. Recrystallization from methanol afforded 0.70 g. of tan crystals, m.p. 239–240° (decomp.): reported, 253° (decomp.) (7). This product was used in the next preparation without attempting further purification.

Ethyl 2-carboxy-7-methoxy-3-indoleacetate. The diacid (0.75 g.) was refluxed one hour with 3 ml. of 0.5% ethanolic hydrogen chloride. Since after four hours no crystals had separated from the cold solution, the solvent was removed at room temperature *in vacuo* over sulfuric acid and potassium hydroxide. The residue (0.82 g.) was crystallized from benzene: 0.70 g., m.p. 146.5–147°. A small sample recrystallized for analysis melted 147–148°. With Ehrlich's reagent this half ester gave a faint green color which changed to greenish yellow on addition of sodium nitrite. A satisfactory analysis was not obtained for this compound.

7-Methoxy-3-indoleacetic acid. A finely ground mixture of 0.60 g. of half ester and 80 mg. of catalyst 39KAF was added to 6 ml. of quinoline contained in a 10-ml. round-bottomed flask which was then connected to a gas burette and immersed in a Wood's metal-bath. Rapid evolution of carbon dioxide began about 210°. When the theoretical volume of gas had been collected, and this coincided with a marked falling-off of the carbon dioxide evolution, the mixture was cooled, stirred with a large volume of ether, filtered, and the filtrate washed with dilute hydrochloric acid, water, aqueous sodium bicarbonate, and aqueous sodium chloride.

After removing the solvent from the dried ethereal extract the dark, oily residue was saponified by mixing thoroughly with 1 ml. of 2 *N* absolute ethanolic potassium hydroxide and allowed to stand one hour. The mixture was diluted with 6 ml. of water and a small amount of oil which separated was removed by ether extraction. Acidification of the aqueous solution produced a heavy brown liquid which, on dissolution in ether and removal of the solvent, gave 0.29 g. of crude brown crystals. Two recrystallizations from hot water afforded about 0.1 g. of pure material, m.p. 127–127.5° (decomp.). With Ehrlich's reagent it furnished a pale blue color which was converted to a more intense reddish violet by the addition of solid sodium nitrite.

Anal. Calc'd for $C_{11}H_{11}NO_3$: C, 64.37; H, 5.40.

Found: C, 64.35; H, 5.40.

m-Anisidine. This was obtained by acetylation of *m*-aminophenol, methylation of the product and hydrolysis with hydrochloric acid (13).

Ethyl 2-carboethoxy-6-methoxy-3-indoleacetate. (a) *Preparation of the m-methoxyphenyl-hydrazone of diethyl α -ketoglutarate.* *m*-Anisidine (9.5 g., 0.077 mole), dissolved in 19 ml. of

concentrated hydrochloric acid and 8 ml. of water, was diazotized at about -5° with 5.3 g. (0.075 mole) of sodium nitrite in 15 ml. of water. When diazotization had been completed the solution was added with agitation to a mixture of 17.2 g. (0.31 mole) of potassium hydroxide in 70 g. of ice and water to which 17.7 g. (0.077 mole) of diethyl α -acetoglutarate had just been added. Then the reddish brown reaction mixture, after acidification with dilute hydrochloric acid, was extracted with ether and the extract washed and dried.

(b) *Cyclization*. The deep red oil remaining after removing all the solvent was cyclized by refluxing for one hour with 45 ml. of 15% ethanolic hydrogen chloride. The yield of product with 10% ethanolic acid was lower. After cooling, dilution with ether, washing, drying, and removal of the solvent the residual, dark viscous reaction product became semi-solid on standing. The crystalline material was advantageously separated from the liquid impurities by drying on porous earthenware: 7.4 g. (32%) of crude ester. Two crystallizations, one from methanol and one from ethanol, furnished 4.4 g. of pure material, m.p. $107.5\text{--}108.5^{\circ}$.

Anal. Calc'd for $C_{16}H_{15}NO_5$: C, 62.95; H, 6.25; N, 4.60.

Found: C, 62.75; H, 6.02; N, 4.65.

2-Carboxy-6-methoxy-3-indoleacetic acid. The 6-methoxyindole diester (3.0 g.) was saponified by refluxing 12 minutes on the steam-bath with 1.3 g. of sodium hydroxide in 15 ml. of 90% ethanol. After cooling, the white, solid salt which had separated was dissolved in 12 ml. of warm water, and acidified with dilute hydrochloric acid: 2.4 g., m.p. 217° (decomp.). Two recrystallizations from 50% acetic acid afforded pure material, m.p. 225° (decomp.): reported, $224\text{--}225^{\circ}$ (8). Exposure to air or prolonged heating of its solutions caused the appearance of green decomposition products.

Anal. Calc'd for $C_{12}H_{11}NO_5$: N, 5.63. Found: N, 5.76.

Ethyl 2-carboxy-6-methoxy-3-indoleacetate. The diacid (1.8 g.) was refluxed with 5 ml. of 0.5 ml. of 0.5% ethanolic hydrogen chloride for thirty-five minutes. On cooling the green solution, crystalline material precipitated: 1.3 g., m.p. $171\text{--}172.5^{\circ}$ (decomp.). Two crystallizations from aqueous ethanol gave pure material, m.p. 176° .

Anal. Calc'd for $C_{14}H_{13}NO_5$: N, 5.05.

Found: N, 5.16, 4.94.

6-Methoxy-3-indoleacetic acid. (a) *Decarboxylation*. An intimate mixture of 0.60 g. of half ester and 0.80 mg. of catalyst 39KAF was heated in 6 ml. of quinoline at $195\text{--}205^{\circ}$ until the theoretical volume of carbon dioxide had been collected. The crude ester was obtained in the customary fashion.

(b) *Saponification*. The crude ester was dissolved in 1.0 ml. of a 2.3 *N* solution of potassium hydroxide in 99% ethanol and allowed to stand at room temperature one hour during which the mixture solidified. After warming three minutes on the steam-bath, the mixture was dissolved in 6 ml. of warm water and made just acid with 1 *N* hydrochloric acid. The precipitated material was collected and dried: 0.21 g. of dark red crystals, m.p. $157\text{--}158^{\circ}$. Two crystallizations from hot water furnished 0.10 g. of cinnamon-colored platelets, m.p. $163\text{--}164^{\circ}$ (decomp.). In a preliminary preparation, this compound was obtained from hot water in apparently pure condition as bluish-green leaflets. Ehrlich's reagent in the cold produced a rather deep blue convertible to a more intense violet by addition of solid sodium nitrite.

Anal. Calc'd for $C_{11}H_{11}NO_3$: N, 6.83.

Found: N, 6.78, 6.88.

Veratrole. This diether, prepared from catechol, was obtained in 93 g. (74%) yield, b.p. $205\text{--}208^{\circ}/760$ mm. (14).

4-Nitroveratrole. Although this preparation was performed twice, the reported yield could not be attained (15). The crude, chocolate-colored material from the nitration of 25 g. of veratrole aggregated 28 g. (82%). Two crystallizations from aqueous ethanol provided 19 g. (55%) of pure material, m. 97.5° .

4-Aminoveratrole. 4-Nitroveratrole (11.0 g., 0.060 mole), dissolved in 200 ml. of ethanol, was catalytically hydrogenated at three atmospheres and room temperature using 0.120 g.

of platinum oxide. The solution of the unstable amine was separated from the catalyst, 50 ml. of benzene added, and the solvents removed through a fractionating column. The dark red residue was distilled in the presence of glass wool: 6.8 g. (74%) of yellowish orange crystals, b.p. 169°/18 mm.

Ethyl 2-carboethoxy-5,6-dimethoxy-3-indoleacetate. (a) *Preparation of the crude 3,4-dimethoxyphenylhydrazone.* 4-Aminoveratrole (6.3 g., 0.041 mole), dissolved in 20 ml. of 6 *N* hydrochloric acid and 20 ml. of water, was diazotized below 0° with 2.8 g. (0.040 mole) of sodium nitrite dissolved in 15 ml. of water. After ten minutes the dark brown solution was added with shaking to a cold solution of 7.4 g. (0.090 mole) of sodium acetate in 65 ml. of 90% ethanol to which 9.2 g. (0.040 mole) of diethyl α -acetoglutarate had just been added. After standing an hour in the cold the reaction mixture was extracted with a large volume of ether, and, after washing and removing the acids from solution, it was dried and the solvent removed, the last traces under diminished pressure.

(b) *Cyclization.* The residual, thick, red oil was refluxed with 42 ml. of 8% ethanolic hydrogen chloride for one-half hour and the cyclization product worked up in the customary manner. After separating from liquid impurities by drying on porous porcelain, the crude crystalline material amounted to 5.1 g. (38%), m.p. 122–124°. One crystallization furnished 4.5 g. (34%) of small pink aciculae, m.p. 126°. Recrystallization failed to improve the melting point. A trace of this ester in glacial acetic acid when treated with a drop of dilute nitric acid gave the brucine color reaction (7). Ehrlich's reagent produced a yellow shade which underwent a transition to green.

Anal. Calc'd for $C_{17}H_{21}NO_6$: C, 60.87; H, 6.31; N, 4.18.

Found: C, 61.05; H, 6.28; N, 4.51.

2-Carboxy-5,6-dimethoxy-3-indoleacetic acid. The pink diester was saponified by gently refluxing 2.0 g. with 15 ml. of 1.2 *N* methanolic sodium hydroxide for fifteen minutes. Addition of 10 ml. of warm water to the orange, alkaline solution followed by acidification and filtration resulted in 1.4 g. of crude material, m.p. 210–211° (decomp.). The filtrate possessed an odor reminiscent of grapefruit juice, this disappearing on addition of bicarbonate. Two crystallizations from glacial acetic acid afforded 0.8 g. of a powder melting indistinctly about 225° (decomp.). A satisfactory analysis for the compound was not obtained.

By-product of the saponification. On standing, the mother liquor from the recrystallization of the diacid acquired an inky opacity, and about 0.3 g. of finely divided material precipitated. Although its melting point and mixed melting point indicated that it was the impure diacid, esterification with 0.5% ethanolic hydrogen chloride resulted in a neutral compound, m.p. 138–141°, which was not obtained from the diacid under these conditions. With Ehrlich's reagent this ester furnished a moderately intense blue.

Anal. Calc'd for $C_{16}H_{18}N_2O_{11}$: C, 59.43; H, 5.99; N, 4.62.

Found: C, 59.54, 59.31; H, 6.02, 6.16; N, 4.52.

Ethyl 2-carboxy-5,6-dimethoxy-3-indoleacetate. The diacid (0.7 g.) was refluxed thirty minutes with 2 ml. of 0.5% ethanolic hydrogen chloride. During this interval the reaction mixture became deep blue. The crystals obtained from the cold solution by scratching aggregated 0.4 g., m.p. 192.5–193.5° (decomp.). Purified by recrystallization from methanol they melted at 195.5° (decomp.) and with Ehrlich's reagent gave a pale blue response converted to green when sodium nitrite was added. The partial saponification of ethyl 2-carboethoxy-5,6-dimethoxy-3-indoleacetate also furnished a small amount of this half ester.

Anal. Calc'd for $C_{15}H_{17}NO_6$: N, 4.56.

Found: N, 4.76, 4.73.

Decarboxylation experiments. The half ester (0.4 g.) intimately mixed with 50 mg. of catalyst 20KAF and 5 ml. of quinoline was submitted to decarboxylation. However, the evolution of gas was extremely sluggish and on working up the product in the customary manner an amount of crude crystalline material was obtained which made purification and identification impossible. With Ehrlich's reagent this gave a deep blue color. A repetition under slightly altered conditions was likewise unsuccessful.

Ethyl 2-carboethoxy-3-naphthazoleacetate. This diester, prepared in 39% yield from α -naphthylamine in the same manner as ethyl 2-carboethoxy-5,6-dimethoxy-3-indoleacetate, crystallized from benzene as pink needles, m.p. 167.5–168.5°. A pale yellowish green was obtained with Ehrlich's reagent.

Anal. Calc'd for $C_{19}H_{19}NO_4$: N, 4.31. Found: N, 4.56.

2-Carboxy-3-naphthazoleacetic acid. A mixture of 3.3 g. (0.010 mole) of diester, 5 ml. of 6 *N* aqueous sodium hydroxide, and 25 ml. of ethanol was refluxed twenty minutes on the steam-bath. After diluting with 25 ml. of water the warm solution was made just acid with hydrochloric acid and filtered. The residue after drying *in vacuo* over potassium hydroxide aggregated 2.7 g. (100%). One crystallization from glacial acetic acid afforded 2.1 g. (78%) of pink, lustrous platelets, m.p. 270° (decomp.). A second crop of 0.2 g. was obtained from the mother liquor. This compound, which formed supersaturated solutions in both ethanol and acetic acid, produced a faint blue color with Ehrlich's reagent and could not be satisfactorily analyzed for nitrogen. Of the five values obtained the last three were with the aid of potassium chlorate to oxidize the sample.

Anal. Calc'd for $C_{18}H_{11}NO_4$: N, 5.20.

Found: N, 4.06, 4.30, 4.33, 4.56, 4.47.

Ethyl 2-carboxy-3-naphthazoleacetate. To 12 ml. of 0.4% ethanolic hydrogen chloride was added 2.1 g. of the diacid, and the mixture refluxed on the steam-bath for one-half hour. On cooling, the product separated as small brown crystals: 1.7 g., m.p. 207.5–208.5°. A second crop amounted to 0.4 g. Recrystallization from ethanol did not improve the melting point. It gave a pale blue color with Ehrlich's reagent which became slowly more intense on warming.

Anal. Calc'd for $C_{17}H_{15}NO_4$: N, 4.71. Found: N, 4.60.

Decarboxylation to ethyl 3-naphthazoleacetate. (a) *Dry run.* A mixture of 0.20 g. of ethyl 2-carboxy-3-naphthazoleacetate and 40 mg. of catalyst 39KAF was ground in a mortar and heated at 220° and 1 mm. in a sublimation assembly immersed in a Wood's metal-bath. The crude material which collected on the cold finger aggregated 40 mg. Three recrystallizations from ethanol gave material melting 107.5° (softened at 101.5°). It gave with Ehrlich's reagent a pale blue in the cold, and this became quite deep on warming, acquiring an inky opacity upon addition of a trace of sodium nitrite.

(b) *Decarboxylation in quinoline.* An intimate mixture of 0.50 g. of half ester and 100 mg. of 39KAF was suspended in 6 ml. of quinoline was heated in a Wood's metal-bath at 195–205° for twenty minutes, when about 85% of the theoretical amount of carbon dioxide had been collected. After cooling, the reaction mixture was diluted with ether, filtered, and washed with dilute hydrochloric acid, water, aqueous sodium bicarbonate, and aqueous sodium chloride. The solution was dried over sodium sulfate, the solvent removed, and the brown crystalline residue distilled at 90–140° at 10^{-4} mm.: 0.25 g. of crude material, m.p. 104.5–106.5°.

Anal. Calc'd for $C_{16}H_{13}NO_2$: N, 5.53. Found: 5.50.

3-Naphthazoleacetic acid. The ethyl ester (0.25 g.) was refluxed 15 minutes on the steam-bath with 1.5 ml. of 1.2 *N* methanolic sodium hydroxide. The reaction mixture was diluted with 2 ml. of water and acidified with dilute hydrochloric acid. The precipitated acid weighed 0.20 g., m.p. 189° (decomp.). Recrystallization from methanol and aqueous ethanol gave pure material, m.p. 194.5° (decomp.). With Ehrlich's reagent it gave a blue color greatly intensified by the addition of sodium nitrite.

Anal. Calc'd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92.

Found: C, 74.90; H, 4.83.

Ethyl 2-carboethoxy-1-naphthazoleacetate. This compound, obtained in 30% yield by the customary procedure, crystallized from benzene as tan needles: m.p. 149°.

Anal. Calc'd for $C_{19}H_{19}NO_4$: N, 4.31.

Found: N, 4.36, 4.46.

2-Carboxy-1-naphthazoleacetic acid. Prepared in the same fashion as the isomeric diacid, this compound crystallized from glacial acetic acid as minute crystals, m.p. 239–240° (de-

comp.). It presented the same analytical difficulties as the isomeric acid. The last three values for nitrogen were obtained using potassium chlorate.

Anal. Calc'd for $C_{16}H_{11}NO_4$: N, 5.20.

Found: N, 4.53, 4.29, 4.86, 4.62, 5.16.

Ethyl 2-carboxy-1-naphthazoleacetate. This compound, obtained in the same manner as isomeric half ester, melted at 219° and furnished a pale greenish blue with Ehrlich's reagent.

Anal. Calc'd for $C_{17}H_{13}NO_4$: N, 4.71. Found: N, 4.69.

Decarboxylation to ethyl 1-naphthazoleacetate. This ester, which can be prepared by either of the methods described for the isomeric compound, crystallized as lustrous brown platelets from ethanol: m.p. 160.5–162.5°.

Anal. Calc'd for $C_{16}H_{13}NO_2$: N, 5.53.

Found: N, 5.24, 5.26.

1-Naphthazoleacetic acid. Obtained by saponification of the ethyl ester and crystallization from hot water, this ester melted at 152–153° (decomp.). Ehrlich's reagent produced a pale blue response which was intensified on warming.

Anal. Calc'd for $C_{14}H_{11}NO_2$: C, 74.69; H, 4.92.

Found: C, 74.39; H, 5.01.

The isomeric monochlorophenylhydrazones of diethyl α -ketoglutarate. These compounds, prepared by the action of the appropriate diazotized amine on diethyl α -acetoglutarate, were obtained initially as reddish orange oils which were transformed to the crystalline phenylhydrazones by the action of ethanolic mineral acids. *m*-Chloroaniline was obtained by hydrogenation of *m*-nitrochlorobenzene at three atmospheres of hydrogen using a platinum oxide catalyst (16). The ortho, meta, and para isomers melted at 120°, 80.5°, and 57.5° respectively.

Anal. Calc'd for $C_{18}H_{19}ClN_2O_4$: Cl, 10.85.

Found: Cl, 10.76, 10.78 (*o*-isomer); 10.58 (*m*-isomer); 10.35, 10.23 (*p*-isomer).

Cyclization experiments. Boiling 14% butanolic sulfuric acid effected elimination of ammonium sulfate from the *m*-chlorophenylhydrazone. However, the organic material isolated could not be purified. Saponification furnished amorphous material soluble in alkali. Ethanolic hydrochloric acid containing zinc chloride and butanolic hydrochloric acid were less effective in producing cyclization.

SUMMARY

The preparation of 5-, 6-, and 7-methoxyindoleacetic acids and 1- and 3-naphthazoleacetic acids by the Japp-Klingemann method for phenylhydrazones, the Fischer indole synthesis, and subsequent transformation reactions is described.

It has been found that much better yields in the Fischer ring closure are obtained with approximately 10% ethanolic hydrochloric acid than with the much higher acid concentrations employed heretofore.

The three isomeric monochlorophenylhydrazones of diethyl α -ketoglutarate could not be successfully cyclized to crystalline indole derivatives.

PRINCETON, N. J.

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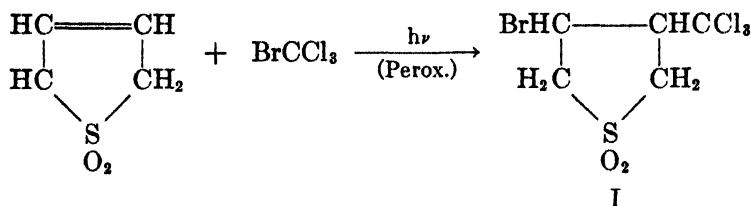
REACTIONS OF ATOMS AND FREE RADICALS IN SOLUTION. XIV. ADDITION OF POLYHALOMETHANES TO BUTADIENE SULFONE

M. S. KHARASCH, M. FREIMAN, AND W. H. URRY

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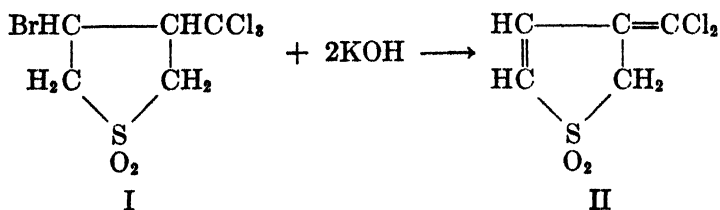
For some time the additions of polyhalomethanes to simple (1) and cyclic (2) olefins have been studied in this laboratory. The present paper deals with the additions of polyhalomethanes to an unsaturated heterocyclic compound, namely, butadiene sulfone (2,5-dihydrothiophene 1-dioxide).

In the presence of light or peroxides (preferably diacyl peroxides) bromotrichloromethane reacts additively with butadiene sulfone to give 3-bromo-4-trichloromethyltetrahydrothiophene 1-dioxide (I),



as well as some sulfur dioxide and an oil containing no sulfur. Since there is no butadiene among the reaction products, the oil is probably a mixture of the 1,4 and 1,2 addition products of bromotrichloromethane to butadiene.¹

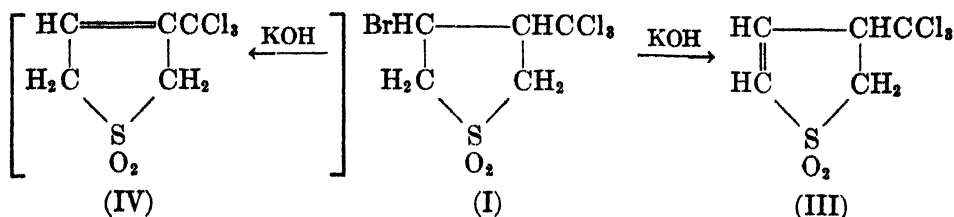
Compound I is a crystalline material which melts at 141–142° (uncorr.). When it is treated in alcoholic solution with potassium hydroxide, two equivalents of base are consumed, and Compound II is formed.



The structure assigned to Compound II is in agreement with its analysis, molecular weight, and absorption spectrum.

When Compound I is treated with less than two equivalents of base, the product is a mixture containing some unchanged material and some Compound II. Probably the first step in the reaction is the removal of the hydrogen bromide to give Compound III; there follows a rapid reaction in which hydrogen chloride is eliminated to give Compound II.

¹ The compounds formed by the addition of bromotrichloromethane to butadiene have been carefully investigated (Kharasch and Nudenberg, unpublished work). Both the 1,2 (15–20%) and 1,4 (80–85%) adducts have been isolated.



The fact that, when I is treated with alkali, III, and not IV, is the compound first formed is of considerable theoretical interest. This subject will be discussed in a future publication dealing with dehydrohalogenation of the adducts of bromotrichloromethane and unsaturated cyclic hydrocarbons (3).

When carbon tetrachloride (instead of bromotrichloromethane) is heated (110°) with butadiene sulfone in an autoclave in the presence of a diacyl peroxide, the products obtained are similar to the ones already described. After six hours heating, 12% of a sulfur-free adduct, (presumably a mixture of 1,1,1,5-tetrachloropentene-2 and 1,1,1,3-tetrachloropentene-1)¹ is obtained. There is also 10% of an adduct of carbon tetrachloride to butadiene sulfone. That the structure of this adduct is similar to that of Compound I is shown by its ready conversion to Compound II by treatment with two equivalents of alcoholic potassium hydroxide. The product thus obtained does not depress the melting point of Compound II prepared from Compound I.

EXPERIMENTAL PART

Reagents. Butadiene sulfone (m.p. 65–66.5°) was prepared from butadiene and sulfur dioxide (4). Bromotrichloromethane was distilled at reduced pressure, and the fraction boiling at 42–43.6°/92 mm., $n_D^{19.2}$ 1.5060, was used.

The photochemical reaction of bromotrichloromethane with butadiene sulfone: the preparation of 3-bromo-4-trichloromethyltetrahydrothiophene 1-dioxide. A suspension of butadiene sulfone (11.8 g., 0.1 mole) in bromotrichloromethane (297.5 g., 1.5 moles) was irradiated by a mercury vapor-neon fluorescent coil in a reaction vessel equipped with a reflux condenser. A slow stream of nitrogen was passed through the reaction mixture. The top of the reflux condenser was connected to a bottle containing sodium hydroxide solution and a trap cooled at –78°. In thirty minutes the temperature of the reaction mixture rose to 70° and the butadiene sulfone dissolved. The solution was irradiated at that temperature for thirteen hours and then cooled. The crystalline material (A) which separated was collected on a filter and washed with 20 cc. of ice-cold bromotrichloromethane. After overnight drying in a desiccator, the material, (12.5 g.; 40% yield), melted at 139–140°. Upon crystallization from ligroin (65–70°), the compound melted at 141–142°.

Anal. Calc'd for $\text{C}_4\text{H}_4\text{BrCl}_3\text{O}_2\text{S}$: C, 18.98; H, 1.91; S, 10.13; Ag equiv., 79.11.

Found: C, 18.87; H, 2.03; S, 9.84; Ag equiv., 79.26.

The filtrate from A was concentrated to a volume of 40 cc. After cooling, large, glassy crystals (B) separated: unchanged butadiene sulfone (1.1 g.; m.p. 65–66°).

The filtrate from B was concentrated under reduced pressure until all the bromotrichloromethane had been removed. The residue was dissolved in ether and cooled. The precipitate (1.8 g., m.p. 53–118°), (C), was crystallized from 95% ethanol and yielded 0.77 g. of material, m.p. 81–130°, (D).

The ethanol filtrate from D was concentrated to dryness, and the residue was triturated with ether. The solid which separated, 0.41 g., m.p. 65–66.5°, (E) proved to be a further amount of unchanged butadiene sulfone.

The ethereal mother liquor from *C* was concentrated until only an oil remained. On distillation, a fraction, 4.95 g., b.p. 62–105°/0.8 mm., (*F*), was obtained. Decomposition was observed during the distillation. After overnight standing, this oil deposited large crystals, which were washed with a small amount of cold ether. The crystalline solid was butadiene sulfone, 0.94 g., m.p. 63.5–65.5°, (*G*). Thus, the total amount of unchanged sulfone amounted to 2.4 g. or 20%.

From the –78° trap connected to the distillation apparatus during the distillation of the oil, a small amount of white crystals, (*H*), of camphor-like odor was recovered. These sublimed at room temperature, and melted with sublimation in a sealed tube at 182–186°. The melting point of a mixture with an authentic sample of hexachloroethane showed no depression.

The sodium hydroxide solution was oxidized by addition of an excess of bromine water. After acidification, the excess bromine was removed. The solution was treated with an excess of barium chloride solution, and the insoluble sulfate was collected and ignited. The barium sulfate collected corresponded to 0.74 g. of sulfur dioxide, or 1.37 g. of butadiene sulfone.

No butadiene was found in the cold trap.

The peroxide-induced addition of bromotrichloromethane to butadiene sulfone: the preparation of 3-bromo-4-trichloromethyltetrahydrothiophene 1-dioxide. Butadiene sulfone (35.4 g., 0.3 mole) was added to bromotrichloromethane (268 g.) and the temperature raised to 80°. At that temperature, the sulfone was completely dissolved. A reflux condenser was attached to the reaction flask, and to the top of the condenser was connected a vessel, containing 1 *N* sodium hydroxide solution, and a trap cooled to –78°. A solution of acetyl peroxide (3.4 g.) in bromotrichloromethane (16 cc.) was added in five portions at thirty-minute intervals while the temperature was maintained at 80–85°. After all the peroxide had been added the solution was maintained for two hours at 85–88°. When the reaction mixture was cooled to 0°, a crystalline solid separated. This precipitate was washed with a small amount of cold bromotrichloromethane. The practically pure crystals proved to be 3-bromo-4-trichloromethyltetrahydrothiophene 1-dioxide (58.5 g., m.p. 138.5–140°, 61.7% yield).

The sodium hydroxide solution was treated with bromine water, and then with barium chloride solution. The weight of barium sulfate which separated corresponded to 1.98 g. of sulfur dioxide, or 3.6 g. of butadiene sulfone.

The bromotrichloromethane mother liquor was concentrated to 40 cc. and cooled overnight at 0°. The solid which crystallized was washed with 5 cc. of ice-cold bromotrichloromethane. The material, slightly impure butadiene sulfone (*K*), weighed 3.6 g. and had the melting point 57–59°.

The filtrate from *K* was concentrated under reduced pressure until all the bromotrichloromethane had been removed. The residue was triturated with 20 cc. of ether, and the solid which separated was washed with a small amount of ether. In this manner, a further amount of impure butadiene sulfone (2.6 g., m.p. 52–57°), (*L*), was obtained.

The ether filtrate from *L* was washed with water to remove the last traces of unchanged sulfone, and was dried over sodium sulfate. The ether was then removed, and the oily residue was distilled in vacuum. Three fractions were collected: (a) 3.0 g., b.p. 50–76°/0.4 mm., n_D^{20} 1.528; (b) 0.5 g., b.p. 76–100°/0.4 mm., n_D^{20} 1.535; (c) 4.0 g., b.p. 100–127°/0.35 mm., n_D^{20} 1.560. These three fractions did not decolorize bromine-carbon tetrachloride solution, but did decolorize potassium permanganate solution. They contained halogen, and did not contain sulfur.¹

The material caught in the cold trap was warmed, and the escaping vapor was allowed to pass into a 5% solution of bromine in carbon tetrachloride. No precipitate of butadiene tetrabromide was obtained, nor was there any solid residue when the whole mixture was evaporated to dryness.

The reaction of the 1:1 addition compound of bromotrichloromethane and butadiene sulfone with potassium hydroxide: the preparation of 3-dichloromethylene-2,3-dihydrothiophene

1-dioxide. A portion of the bromotrichloromethane-butadiene sulfone addition product (2.75 g.) was dissolved in absolute alcohol (100 cc.), two drops of phenolphthalein solution was added, and the resulting solution was titrated with 0.45 *N* ethanolic potassium hydroxide until the appearance of a permanent pink color; 38.75 cc. of the potassium hydroxide solution was required (calculated for two equivalents of hydrohalogen acids, 38.66 cc.). A white solid (a mixture of KBr and KCl) separated and was washed with cold ethanol. The filtrate was concentrated to a volume of 10 cc. When the solution was cooled to 5°, a crystalline solid precipitated. This was washed with cold ethanol and dried in a desiccator overnight (1.45 g., 84% yield; m.p. 110–111.5°). The melting point of this material was not altered by crystallization from ether.

Anal. Calc'd for $C_6H_4Cl_2O_2S$: Cl, 35.63; mol. wt., 199.

Found: Cl, 35.04; mol. wt., 203.

The dichloro compound did not decolorize bromine, but did decolorize potassium permanganate solution very rapidly; it gave no precipitate with boiling alcoholic silver nitrate solution.

When the bromotrichloromethane-butadiene sulfone adduct was treated with one molecular equivalent of ethanolic potassium hydroxide, about 25% of unchanged material was recovered. Upon concentration of the solution, a material which melted at 89–97° was obtained (50%, by weight, of the adduct used). The melting point of this material was not changed by successive crystallizations. It is probably a mixture of butadiene-sulfone bromotrichloromethane adduct, and Compound II.

The reaction of butadiene sulfone with carbon tetrachloride in the presence of benzoyl peroxide in a steel autoclave. A suspension containing butadiene sulfone (35.4 g., 0.3 mole), carbon tetrachloride (185 g., 1.2 moles), benzoyl peroxide (0.6 g.) was heated for six hours at 110° in a steel autoclave. When this temperature was first attained, the pressure within the autoclave was 101 lbs./sq. in. The apparatus was allowed to cool to room temperature, and the excess pressure was released. The odor of sulfur dioxide was observed.

The dark reaction mixture was subjected to steam distillation. The lower organic layer of the distillate was separated, and the upper aqueous layer was extracted with 50 cc. of carbon tetrachloride. The combined organic extracts were dried over sodium sulfate, and the excess solvent was removed at atmospheric pressure. The residue was distilled in a vacuum, and the fraction (9.0 g.) boiling at 126–148°/57 mm. was collected. A redistillation of this material gave a fraction (7.2 g.; 12% yield) which boiled at 76–79°/5 mm., 127–129°/60 mm.; n_D^{20} 1.5060.

The residue which remained from the steam distillation, together with the water which had condensed during the steam distillation, was brought to a boil and filtered. On cooling, the filtrate deposited crystals, 1.66 g., m.p. 125–126°. Upon crystallization from methanol, the compound melted at 126.5–127.5°. This material gave strong positive tests for sulfur and chlorine.

A second quantity of crystals was obtained by extracting the residue from the dark reaction mixture with more boiling water. The filtered aqueous solution gave crystals, 0.8 g., m.p. 120–125°.

A third amount of material was obtained by powdering the remaining residue and shaking the dark powder with 200 cc. methanol at room temperature. The mixture was filtered, and the methanolic filtrate was concentrated to a small volume. After cooling to 0°, light brown crystals (6.2 g., m.p. 118.5–123°) separated. The material was dissolved in ether and boiled after the addition of activated carbon. From the ether filtrate, upon concentration, a white crystalline solid which melted at 125.5–127° was obtained. This material did not depress the melting point of the material previously isolated. The total weight of this substance was 8.7 g.

This crystalline material was shown to be an addition product of one mole of carbon tetrachloride to one mole of butadiene sulfone by the following experiment.

The reaction of the carbon tetrachloride-butadiene sulfone addition product with ethanolic potassium hydroxide. A portion of the solid product obtained in the above reaction (0.42

g., m.p. 126.5–127.5°) was dissolved in ethanol (50 cc.), two drops of phenolphthalein solution was added, and the solution was titrated with 0.446 *N* ethanolic potassium hydroxide; 6.92 cc. (0.174 g. potassium hydroxide) was required (calculated for two equivalents of hydrogen chloride, 0.173 g.). The ethanol was removed under vacuum, and the residue was dissolved in ether and filtered. The ether filtrate was concentrated to 2 cc. On overnight standing, crystals separated, which were washed with a little ice-cold ether and dried. White crystals melting at 110–111° were thus obtained. This material did not depress the melting point of the compound formed by the action of two equivalents of potassium

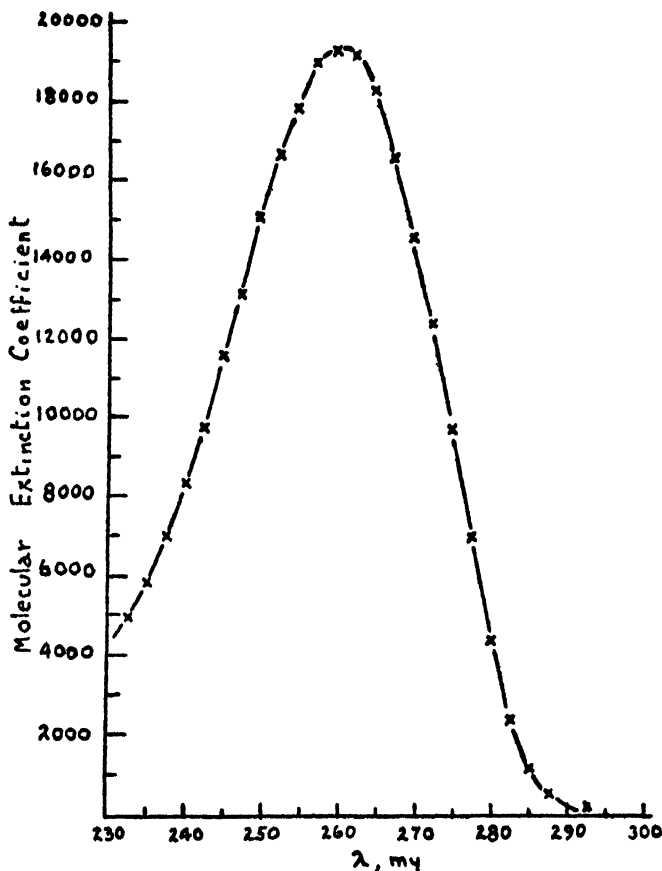


FIGURE 1. ABSORPTION SPECTRUM OF COMPOUND II IN ISOPROPANOL

hydroxide with one equivalent of 3-bromo-4-trichloromethyltetrahydrothiophene 1-dioxide (Compound II).

Absorption spectra. The spectra were determined with a Beckman quartz spectrophotometer, density readings being made at 5-mμ intervals, except in the region of a maximum where the readings were made at 1-mμ intervals.

The solvent used was 99% isopropanol (Carbide and Carbon). The concentration of the 3-dichloromethylene-2,3-dihydrothiophene 1-dioxide was 5.36 mg. per liter; that of the butadiene sulfone was 6390 mg. per liter, and that of the 3-bromo-4-trichloromethyltetrahydrothiophene 1-dioxide was 390 mg. per liter.

The absorption spectra of butadiene sulfone and 3-bromo-4-trichloromethyltetrahydrothiophene 1-dioxide are not given in Figure 1 since their absorption in the range from 2300

Å to 3000 Å is almost negligible. Butadiene sulfone gave a molecular extinction coefficient of 3.7 at 2300 Å, and its absorption dropped to a molecular extinction coefficient of 0.19 at 3000 Å. 3-Bromo-4-trichloromethyltetrahydrothiophene 1-dioxide showed a gradual fall in molecular extinction coefficient from 135 at 2300 Å to 6 at 3000 Å.

SUMMARY

1. The peroxide-induced and photochemical reactions of bromotrichloromethane with butadiene sulfone yield a one-to-one addition product, namely, 3-bromo-4-trichloromethyltetrahydrothiophene 1-dioxide.

2. The peroxide-induced reaction of carbon tetrachloride with butadiene sulfone yields a similar adduct, namely, 3-chloro-4-trichloromethyltetrahydrothiophene 1-dioxide.

3. The 3-halo-4-trichloromethyltetrahydrothiophene 1-dioxides, when treated with two molecular equivalents of alcoholic potassium hydroxide, yield 3-dichloromethylene-2,3-dihydrothiophene 1-dioxide.

4. A free-radical chain reaction is postulated to account for formation of the adducts from butadiene sulfone and polyhalomethanes.

CHICAGO 37, ILL.

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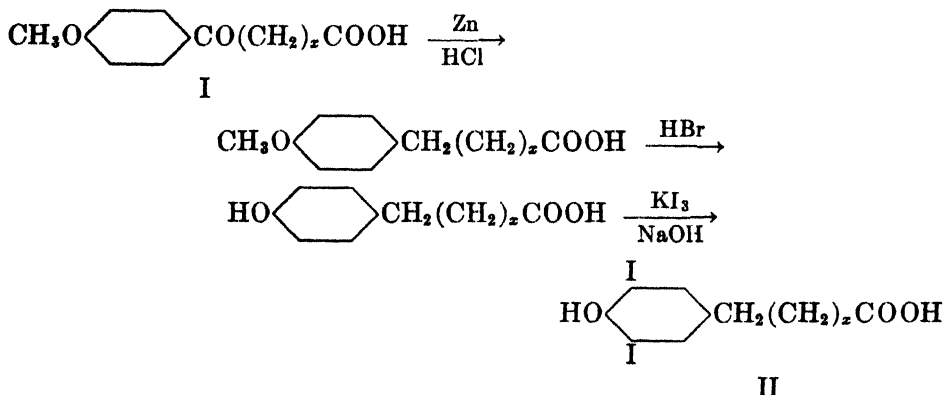
THE PREPARATION OF SOME IODINATED
PHENYLALKANOIC ACIDS

M. G. PRATT, J. O. HOPPE, AND S. ARCHER

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Some years ago we were interested in preparing a series of ω -diiodohydroxy-phenylalkanoic acids for testing as radiopaques in cholecystography. This report is prompted by the appearance of a patent by Natelson (1) and a paper by Papa, Schwenk, and Hankin (2).

Natelson outlined the method of synthesis we employed but failed to indicate yields or physical properties of his products. Papa *et al.*, on the other hand, described excellent procedures for the intermediate steps and we wish to supplement some of their observations. The iodinated acids were prepared according to the following equations:



The preparation of δ -anisoylvaleric acid (I, $x = 4$) was studied in some detail. In agreement with Papa it was found that the condensation between anisole and δ -carbomethoxyvaleroyl chloride in carbon disulfide gave impure keto acid. We were able to isolate δ -(*p*-hydroxybenzoyl)valeric acid by alkali extraction of the crude reaction product, an indication that considerable ether cleavage had occurred. The major product, which melted over a wide range at about 70° , was probably a mixture of the desired methoxy acid and the cleavage product. The hydroxy keto acid was prepared from phenol and carbomethoxyvaleroyl chloride by a procedure similar to that used by Ralston for the reaction between phenol and higher fatty acid chlorides (3). Mixed melting point determinations showed the substances to be identical.

The condensation between anisole and polyadipic anhydride was carried out according to Plant and Tomlinson (4). We were able to isolate δ -anisoylvaleric acid and 1,4-dianisoylbutane in 33 and 47% yields, respectively, based on the anisole.

Although Papa and co-workers found that no cleavage occurred in their

condensation between anisole and δ -carboethoxyvaleroyl chloride at low temperature in tetrachloroethane, under our conditions, which were very similar, we had evidence that this side reaction did occur to some extent. Thus in a typical run in a mixed solvent (20% nitrobenzene, 80% tetrachloroethane) there was obtained a crude acid which melted below 90°. Several recrystallizations were required to raise the melting point above 120°. However, when the material was dissolved in dilute sodium hydroxide and treated with methyl sulfate the substance obtained by acidification melted at 118–120° and needed only one crystallization to reach analytical purity. In every case methylation raised the melting point of the crude acid.

β -Anisoylpropionic and γ -anisoylbutyric acids were prepared from succinic and glutaric anhydrides, respectively, by the excellent procedure of Fieser (5). It is doubtful whether the method of the Schering workers (2) offers any advantage here since two additional steps are required for the preparation of the acid chlorides.

The ω -anisoylalkanoic acids were reduced by the Clemmensen method and then demethylated in hydrobromic acid-acetic acid solution (2).

In pilot experiments on the iodination of ω -(*p*-hydroxyphenyl)caproic acid by the potassium triiodide-sodium hydroxide method it was found advisable to avoid using even a slight excess of reagent. After completion of the iodination the diiodo acid was precipitated as an almost white powder by passing sulfur dioxide *slowly* through the solution to pH 2. Rapid acidification usually resulted in the separation of an almost intractable gum.

The direct iodination of δ -anisylvaleric acid in acetic acid solution with iodine monochloride yielded only the monoiodo acid despite the large excess of halogenating agent. Similarly γ -anisylbutyric acid gave γ -(3-iodo-4-methoxyphenyl)butyric acid.

Pharmacology. In experimental animals visualization of the gall bladder was achieved by oral administration of the three 3,5-diiodo-4-hydroxyphenylalkanoic acids (II, $x = 2, 3, 4$). In agreement with Epstein, *et al.* (6) it was found that the caproic acid gave more intense shadows than the lower homologs. However, the substance did not seem to offer any advantages over iodoalphonic acid [α -phenyl- β -(3,5-diiodo-4-hydroxyphenyl)propionic acid]. Preliminary toxicity data indicate the oral L.D.₅₀ in mice of the three substances lie within the range 2–4 g./kg.

Acknowledgment. We wish to thank Mr. John Romano for technical assistance.

EXPERIMENTAL

δ -(*p*-Hydroxybenzoyl) valeric acid. To a solution of 28 g. (0.3 mole) of phenol in 60 ml. of dry chlorobenzene cooled to 10° was added 40 g. of aluminum chloride, keeping the temperature below 15°. Then 35.6 g. of δ -carbomethoxyvaleroyl chloride was added dropwise over a period of one hour. The mixture was heated at 60° for six hours and then hydrolyzed by pouring onto iced hydrochloric acid. The layers were separated and the water washed with benzene. The combined oil layers were subjected to steam distillation. The residual oil was separated from the water and then washed with a solution of dilute alcoholic sodium

hydroxide (3.0 g. of sodium hydroxide in 160 ml. of water and 40 ml. of ethanol). The basic extract was acidified to precipitate an oil, which upon saponification and subsequent acidification gave the hydroxy keto acid; wt. 17 g. After recrystallization from methanol it melted at 149–150°.

Anal. Calc'd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35.

Found: C, 64.14; H, 6.12.

δ -Anisoylvaleric acid: From *δ -carbomethoxyvaleroyl chloride*. To a mixture of 43.2 g. of anisole and 71 g. of *δ -carbomethoxyvaleroyl chloride* in 400 ml. of tetrachloroethane and 100 ml. of nitrobenzene cooled to 0–5° was added 167 g. of aluminum chloride over a period of ninety minutes. The whole was stirred at this temperature for three hours and left overnight. The mixture was poured onto dilute hydrochloric acid and ice and subjected to steam distillation. The residue was separated from the water and saponified with dilute sodium hydroxide. On acidification there was precipitated 85 g. of crude keto acid (90%). It melted at 87–107°. The whole was taken up in dilute sodium hydroxide and treated with 30 ml. of methyl sulfate at 60°. The acid which separated on acidification now melted at 118–122°. After recrystallization from methanol the acid weighed 75 g. (79%); m.p. 122–124°; [lit. value (2) 128°].

From polyadipic anhydride. A solution of 73 g. of adipic acid in 300 ml. of acetic anhydride was refluxed for six hours, and concentrated to dryness *in vacuo*. The polyanhydride was treated with a mixture of 52.5 ml. of anisole, 120 ml. of nitrobenzene and 480 ml. of tetrachloroethane and cooled to 0°. Aluminum chloride (135 g.) was added portionwise to the stirred, cooled solution over a period of two hours. The mixture was left at 5° for two days before being hydrolyzed with ice and hydrochloric acid. After steam distillation the residue was separated from the water, and thoroughly extracted with 10% sodium carbonate solution. The basic extracts were acidified and the solid that separated was methylated and reprecipitated to give 34 g. (33%) of the methoxy acid, m.p. 118–121°. The neutral fraction, which was 1,4-dianisoylbutane, amounted to 37 g. (47%), and melted at 140–142° after recrystallization from alcohol. Plant and Tomlinson (4) who carried out the reaction in carbon disulfide reported m.p. 144° for dianisoylbutane.

γ -Anisoylbutyric acid. The procedure described by Fieser was used for the next higher homolog. From 43.2 g. of anisole was obtained 73 g. of methoxyketo acid (82%). After three recrystallizations from methanol the acid melted at 138–140°; [Papa (2) reported 138–139°].

Anal. Calc'd for $C_{13}H_{16}O_4$: C, 64.85; H, 6.35.

Found: C, 64.82; H, 6.43.

*δ -(*p*-Hydroxyphenyl)valeric acid.* A solution of 38.6 g. of *δ -anisylvaleric acid* (2), 485 ml. of 48% hydrobromic acid, and 100 ml. of acetic acid was refluxed for fifteen hours, boiled with charcoal, filtered, and cooled. The solid that separated was crystallized twice from dilute ethanol to yield 24 g. (67%), m.p. 117–119°.

Anal. Calc'd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26.

Found: C, 68.07; H, 7.06.

δ -(3,5-Diiodo-4-hydroxyphenyl)valeric acid. A solution of 19.4 g. of *δ -(*p*-hydroxyphenyl)-valeric acid* in 400 cc. of 1 *N* sodium hydroxide was stirred at room temperature, and a solution of 565 ml. of potassium triiodide which contained 51 g. of iodine was added dropwise over a period of 45 minutes. After one-half hour sulfur dioxide was bubbled through slowly to pH 2. The granular solid, which weighed 41 g. and melted at 117–122°, was filtered and washed with water. After two crystallizations from acetic acid and one from toluene there was obtained 24 g. (63%) of pure acid, m.p. 124–126°.

Anal. Calc'd for $C_{11}H_{12}I_2O_3$: C, 29.62; H, 2.71.

Found: C, 29.88; H, 2.62.

The iodination of the corresponding butyric and caproic acids was carried out similarly.

ω -(3,5-Diiodo-4-hydroxyphenyl)caproic acid. Obtained in 58% yield after recrystallization from methanol; m.p. 117–119°.

Anal. Calc'd for $C_{13}H_{14}I_2O_3$: C, 31.33; H, 3.07.

Found: C, 31.40; H, 3.14.

γ -(3,5-Diiodo-4-hydroxyphenyl)butyric acid. Obtained in 72% yield after recrystallization from dilute acetic acid; m.p. 105–107°.

Anal. Calc'd for $C_{10}H_{10}I_2O_3$: C, 27.80; H, 2.33.

Found: C, 27.90; H, 2.33.

δ -(3-Iodo-4-methoxyphenyl)valeric acid. Thirty grams of δ -anisylvaleric acid was dissolved in 100 ml. of acetic acid and warmed to 80°. A solution of 10.5 ml. of iodine monochloride in 25 ml. of acetic acid was added in one portion to the hot solution and the whole stirred for 30 minutes as 100 ml. of water was added dropwise. At the end of the time the hot solution, from which the iodo acid started to separate, was cooled to 10° and sulfur dioxide was bubbled in to discharge the color. The acid was filtered and recrystallized from ethanol to give long needles, m.p. 143–145°, wt. 40 g. (83%). One more crystallization raised the m.p. to 146–148°.

Anal. Calc'd for $C_{12}H_{15}IO_3$: I, 37.98. Found: I, 38.18.

Similarly γ -(3-iodo-4-methoxyphenyl)butyric acid was obtained in 77% yield, m.p. 105–107° after crystallization from benzene-ligroin.

Anal. Calc'd for $C_{11}H_{13}IO_3$: I, 39.7. Found: I, 40.6.

SUMMARY

1. ω -(3,5-Diiodo-4-hydroxyphenyl) butyric, valeric, and caproic acids have been prepared by the iodination of the corresponding hydroxy acids.

2. Iodination of two of the corresponding methoxy acids gave only the mono-iodo derivatives.

RENSSELAER, N. Y.

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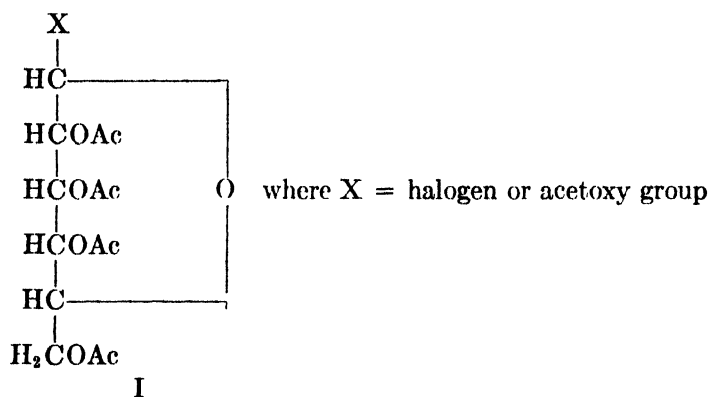
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**2,3,4,5-TETRAACETYLADONITOL AND 1-CHLORO-1-DESOXY-
2,3,4,5-TETRAACETYLADONITOL**

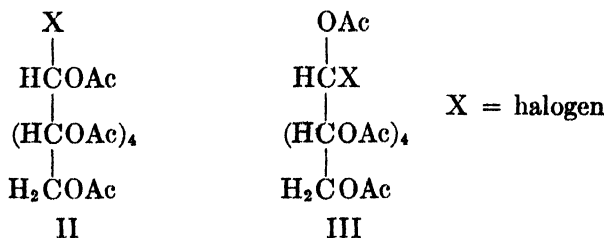
H. HERBERT FOX

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In 1870, Colley (1) prepared acetochloroglucose, the first aceto-halogen sugar by acetylating glucose with acetyl chloride. Since that time many aceto-halogen sugars have been made and have found application in the synthesis of glycosides by the Koenigs-Knorr reaction (2). It is now generally known that, with few exceptions (3, 4, 5) sugar acetates or aceto-halogen sugars prepared by direct acetylation have the lactol or cyclic hemiacetal structure (formula I).



The acyclic or aldehydo sugar acetates have been prepared, in the main, by indirect methods. For example, Wolfrom (6) prepared the acyclic aldehydo glucose pentaacetate by hydrolysis of the acetylated glucose ethylmercaptal with mercuric chloride in the presence of cadmium carbonate. The same compound was obtained by Cook and Major (7) upon catalytic reduction of penta-acetylgluconyl chloride. Halogenation of the aldehydo sugar acetates was effected by Wolfrom and his co-workers (8, 9, 10, 11), who found that treatment of the acyclic sugar acetates with acyl halides produced acyl halide-carbonyl addition compounds (formulas II and III).



In the light of the work already done in the field of aceto-halogen sugars and in view of their importance in sugar chemistry it is remarkable that almost nothing

is known of related sugar alcohols. When, during the course of an investigation in these laboratories some years ago, it became necessary to prepare an acetylated sugar alcohol with a halogen on carbon 1, it was noted that there was an almost complete absence of such compounds in the literature. A dichlorohydrin of mannitol tetraacetate melting at 128–130° was reported by Griner (12), and another dichlorohydrin of mannitol tetraacetate melting at 214° was obtained by Fischer and Armstrong (13). A dulcitol chlorohydrin pentaacetate was also reported by Bouchardat (14) who made it by refluxing dulcitol with 6–8 moles of acetyl chloride. In all these compounds, the positions of the halogens were undefined.

In the present study, it was decided to prepare 1-chloro-1-desoxy-2,3,4,5-tetraacetylodonitol by reducing *aldehydo*-tetraacetyl-D-ribose (15) to adonitol and then halogenating it with an appropriate chlorinating agent. Accordingly, *aldehydo*-tetraacetyl-D-ribose was treated with hydrogen at low pressure and room temperature in the presence of platinum oxide, but no reduction took place. With Raney nickel under the same conditions, however, the reduction went smoothly to give the desired 2,3,4,5-tetraacetylodonitol in the form of soft white needles melting at 55–57°. The ease of reduction is noteworthy, since (Gardner (16) in attempting to reduce *aldehydo*-D-glucose and *aldehydo*-D-galactose pentaacetates to sorbitol and dulcitol pentaacetates respectively experienced considerable difficulty, and was ultimately unsuccessful. He found for example, that manganese dioxide on kieselguhr, and platinum oxide in various solvents and at high temperatures and pressures would not effect reduction. With the use of nickel catalyst on kieselguhr or Raney nickel at temperatures between 150–165° and pressures of 1800 lbs. he obtained reduction and simultaneously, partial deacetylation.

Tetraacetylodonitol is the second acetylated adonitol to be reported. The pentaacetyl derivative was obtained as a non-crystallizable syrup by direct acetylation of the alcohol (17, 18).

Halogenation of the tetraacetylodonitol was effected with thionyl chloride, phosphorus pentachloride, and titanium tetrachloride. Phosphorus trichloride was tried unsuccessfully. The desired 1-chloro-1-desoxy-2,3,4,5-tetraacetylodonitol was obtained as a clear, colorless, viscous liquid which partially solidified on standing. In addition to the desired product, a small quantity of a white crystalline material, m.p. 134–134.5° was obtained in every instance. The analysis:—C, 47.8; H, 6.3; Cl, 10.5; acetyl, 49.8 corresponds reasonably to the empirical formula $C_{14}H_{21}ClO_8$ (theory: C, 48.0; H, 6.0; Cl, 10.1; acetyl, 48.7). A sample of this material on standing in a capped amber bottle for about four years has partially liquefied and possesses a strong odor of acetic acid.

ACKNOWLEDGMENT

The author wishes to acknowledge his gratitude and appreciation to Dr. H. M. Wuest for his helpful suggestions during the course of this work and his indebtedness to Dr. A. Steyermark for the microanalyses. Thanks are also due Charles Pfizer and Co. for a generous supply of *aldehydo*-tetraacetyl-D-ribose.

EXPERIMENTAL

All melting points are corrected and boiling points uncorrected.

2,3,4,5-Tetraacetyladonitol. Thirty grams of *aldehydo*-tetraacetyl-D-ribose dissolved in approximately 100 cc. of purified dioxane was reduced with hydrogen in the presence of Raney nickel catalyst. The reduction was carried out at 30 lbs. pressure and at room temperature, though on several occasions it was found advisable to apply mild heat (50°) to ensure complete reduction. When the theoretical quantity of hydrogen had been taken up, the reaction mixture was filtered and the dioxane was removed under vacuum to yield 28.5 g. (95%) of a syrup which gave no test with Shaffer-Hartmann solution. The syrup was heated with petroleum ether, and on cooling, long, fine white needles appeared. The crystalline product was dissolved in ethanol, treated with Norit, filtered, and evaporated on a steam-bath. The syrupy residue on standing in the refrigerator crystallized in long soft needles melting at 55–57°. The product was soluble in water and the common organic solvents.

Anal. Calc'd for $C_{11}H_{20}O_9 \cdot \frac{1}{2} H_2O$: Acetyl, 52.3. Found: Acetyl, 52.1.

$[\alpha]_D^{25} - 7.4^\circ$, c, 5% in water

1-Chloro-1-desoxy-2,3,4,5-tetraacetyladonitol. (A) *With thionyl chloride.* Tetraacetyladonitol was warmed on the steam-bath with an excess of thionyl chloride for several minutes. The thionyl chloride was then removed under vacuum and the residue was distilled to yield a clear, colorless, viscous distillate, b.p. 150° at 0.6–0.7 mm. On standing, a slight precipitate appeared in the distillate. The precipitate, like the distillate, was insoluble in water. To effect a separation, the mixture was dissolved in a little hot methanol. On cooling, a microcrystalline solid appeared. The precipitate was filtered off and the filtrate was concentrated under vacuum to a clear syrup. The syrup was distilled, b.p. 134–136° at 0.2 mm., n_D^{25} 1.450; $[\alpha]_D$ insignificant in methanol, chloroform, dioxane, acetone, and ethyl acetate.

Anal. Calc'd for $C_{11}H_{19}ClO_8$: C, 46.0; H, 5.6; Cl, 10.2.

Found: C, 45.9; H, 5.8; Cl, 10.3.

The precipitate on recrystallization from methanol was obtained as white rhomboids, m.p. 134–134.5°.

(B) *With phosphorus pentachloride.* Eighty-five grams of the adonitol tetraacetate dissolved in dry chloroform was treated with phosphorus pentachloride portionwise. A vigorous reaction took place with the evolution of hydrogen chloride. When the further addition of phosphorus pentachloride failed to yield a strong effervescence of hydrogen chloride, the reaction was considered complete. A total of 56 g. of phosphorus pentachloride (slightly in excess of the theoretical quantity) was required. The chloroform solution was then washed with ice-water, sodium bicarbonate solution, and finally more ice-water. The neutral chloroform layer was then dried over anhydrous sodium sulfate, filtered, and the chloroform removed under vacuum. The oily residue was distilled; b.p. 146–150° at 0.4–0.5 mm., n_D^{25} 1.451; yield 65.5 g. On standing, the clear distillate yielded a slight precipitate. Separation was effected as previously described and on recrystallization from methanol the solid melted at 134–135° and proved to be identical with the rhomboids reported above.

(C) *With titanium tetrachloride.* Five grams of adonitol tetraacetate dissolved in 35 g. of dry chloroform was treated with 3 g. of titanium tetrachloride in 12 g. of dry chloroform. Heat was evolved and a yellow precipitate appeared which dissolved on shaking. The reaction mixture was heated in a water-bath under reflux for 3 hours. After cooling, the chloroform solution was washed and dried as before and the chloroform was removed under vacuum. The residual syrup promptly showed signs of precipitation. It was therefore separated from the solid in the usual manner before distillation. The solid, on recrystallization, melted at 133.5–134.5°. The distillate was the desired adonityl chloride.

SUMMARY

This report concerns the preparation of 2,3,4,5-tetraacetyladonitol by the catalytic reduction of the corresponding *aldehydo*-tetraacetyl-D-ribose and the preparation of 1-chloro-1-desoxy-2,3,4,5-tetraacetyladonitol by chlorination of the adonitol.

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BACTERICIDAL PHENOLIC INVERT SOAPS¹

JOSEPH B. NIEDERL, GEORGE M. SIEGER, JR. AND FRANK E. STIRN

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INTRODUCTION

In the capillary-active and water-soluble "invert soaps" containing a free phenolic hydroxyl group reported previously by Niederl and Abbruscato (1) and Bruson (2), the bactericidal action was reduced almost to the vanishing point. The decreased bactericidal activity (3) was believed due to the fact that the phenolic nucleus was attached directly to the quaternary ammonium nitrogen. Proceeding on this assumption, a new series of "phenolic invert soaps", having a halogenated, alkylated phenolic nucleus removed from the quaternary nitrogen by an aryloxy polyalkylene ether side chain was prepared. In the new series, it was believed that theoretically improved antibacterial activity ~~might be~~ result, since the phenolic and quaternary ammonium functional groups would be separated sufficiently by the polyalkylene ether bridge to act more independently, and to effect an intramolecular synchronization of desirable properties.

The starting point for the synthesis of the new series of "phenolic invert soaps" was 4-($\alpha, \alpha, \gamma, \gamma$ -tetramethyl)butyl-1,3-dihydroxybenzene, or 4-*tt*-octylresorcinol (I), described initially by J. B. Niederl and co-workers (4, 5). A number of derivatives of I, including nitro, benzoyl, and halo compounds, were prepared. One of the most important of these is 6-chloro-4-*tt*-octylresorcinol (II), which was obtained by chlorinating the initial compound I with sulfuryl chloride in carbon tetrachloride solution. This halogenated alkylresorcinol was found to be a powerful germicide (phenol coefficients, 625 against *Staph. aureus*, and 100 100 against *E. coli*). In addition compound II was found to possess low toxicity in spite of its potent antiseptic, bactericidal and fungicidal properties. 6-Chloro-4-*tt*-octylresorcinol was characterized further by the preparation of a number of derivatives, including the monobenzoyl (II a) and the methylene-bis (II b) derivatives.

Most outstanding of the derivatives of II are the ring-halogenated, phenolic, cationoidic capillary-active and highly bactericidal "invert soaps". These are prepared by treating II with β, β' -dichlorodiethyl ether in an aqueous alkaline medium according to the method of Bruson (6, 7) to form 6-chloro-4-($\alpha, \alpha, \gamma, \gamma$ -tetramethyl)butyl-1-hydroxy-3-phenoxyethoxyethyl chloride (III). On treating the phenolic chloro ether (III) with various tertiary amines at 160–180°, the corresponding quaternary ammonium salts, N-3-[6-chloro-4-($\alpha, \alpha, \gamma, \gamma$ -tetramethyl)butyl-1-hydroxy]phenoxyethoxyethyl ammonium salts are formed.

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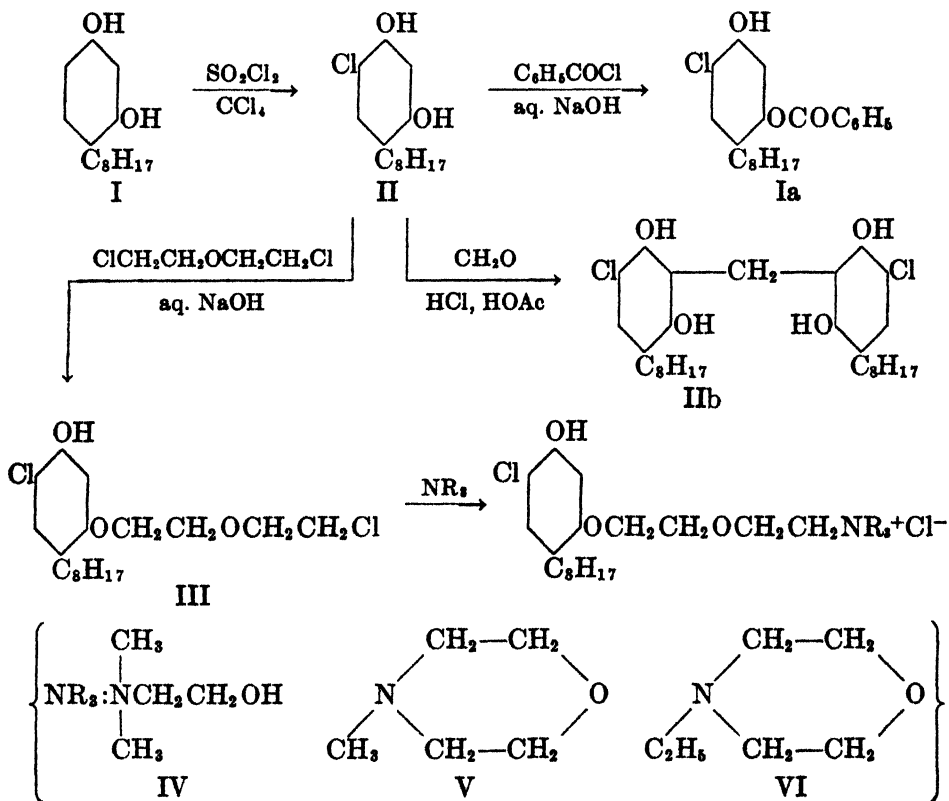
TABLE I
DERIVATIVES OF 4-*tt*-OCTYLRESORCINOL

NO.	COMPOUND	MP (°C.)	BP (°C.)	FORMULA	% C		% H		% NITROGEN		% HALOGEN	
					Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
I	4- <i>tt</i> -Octylresorcinol	107-108	215-220 20 mm.	$C_{14}H_{22}O_2$	75.62	75.57	9.98	10.11				
Ia	Monobenzoate (1-benzoyl)	170-171.5		$C_{21}H_{24}O_3$	77.27	77.33	8.03	8.24				
Ib	Dibenzoate	146-147.5		$C_{28}H_{30}O_4$	78.11	78.31	7.02	7.24				
Ic	Di-(<i>p</i> -nitrobenzoate)	154-155.5		$C_{28}H_{22}N_2O_8$	64.60	64.59	5.42	5.82	5.38	5.60		
Id	1-Benzoyl-6-nitro deriv.	202-203		$C_{21}H_{22}NO_6$	67.88	67.77	6.78	7.00	3.77	3.93		
Ie	1-Benzoyl-2,6-dinitro deriv.	124-125		$C_{21}H_{14}N_2O_7$	60.57	60.78	5.81	6.20	6.72	6.95		
If	1-Benzoyl-6-bromo deriv.	143-144.5		$C_{21}H_{23}BrO_2$	62.22	61.94	6.22	6.21			19.72	20.01
Ig	6-Nitro deriv.	142-143		$C_{14}H_{21}NO_4$	62.90	62.71	7.92	7.84	5.25	5.30		
II	6-Chloro deriv.	88-89		$C_{14}H_{21}ClO_2$	65.48	65.12	8.24	7.92			13.81	13.77
IIa	3-Benzoyl-6-chloro deriv.	147-148.5		$C_{21}H_{23}ClO_3$	69.89	69.93	6.98	7.04			9.83	9.54
IIb	Methylene-bis-6-chloro deriv. or [2,2',6,6'-tetrahydroxy, 3,3'-di-chloro-5,5'-di-(<i>tt</i> -octyl)diphenyl-methane]	186-187.5		$C_{28}H_{42}Cl_2O_4$	66.27	66.64	8.06	8.15			13.49	13.90
III	1-Hydroxy-4- <i>tt</i> -octyl-6-chloro-3-phenoxyethoxyethyl chloride	87-88	175-205 3 mm.	$C_{18}H_{24}Cl_2O_3$	59.50	59.75	7.77	7.77			19.52	20.10
IV	N-(1-Hydroxy-4- <i>tt</i> -octyl-6-chloro-3-phenoxy-ethoxy ethyl)N,N-dimethyl-N-β-hydroxyethylammonium chloride	120-122		$C_{22}H_{30}Cl_2NO_4$					3.10	3.35		
V	N-[1-Hydroxy-4- <i>tt</i> -octyl-6-chloro-3-phenoxyethoxyethyl]-N-methylmorpholinium chloride	80-82		$C_{22}H_{30}Cl_2NO_4$					3.07	3.17		
VI	N-[1-Hydroxy-4- <i>tt</i> -octyl-6-chloro-3-phenoxyethoxyethyl]-N-ethylmorpholinium chloride	83-85		$C_{24}H_{34}Cl_2NO_4$					2.92	2.55		

TABLE II
BACTERIOLOGICAL REPORTS
These tests were run according to the F.D.A. Method at 20°C.

NO.	COMPOUND	PHENOL COEFFICIENT	
		<i>E. typhosa</i>	<i>Staph. aureus</i>
I	4- <i>tt</i> -Octylresorcinol	31	500
Ig	6-Nitro-4- <i>tt</i> -octylresorcinol	20	67
II	6-Chloro-4- <i>tt</i> -octylresorcinol	100	625
IV	N-[3-(6-Chloro-4- <i>tt</i> -octyl-1-hydroxy)phenoxyethoxyethyl]-N,N-dimethyl-N- β -hydroxyethylammonium chloride	200	166
V	N-[3-(6-Chloro-4- <i>tt</i> -octyl-1-hydroxy)phenoxyethoxyethyl]-N-methylmorpholinium chloride	160	133
VI	N-[3-(6-Chloro-4- <i>tt</i> -octyl-1-hydroxy)phenoxyethoxyethyl]-N-ethylmorpholinium chloride	160	133

CHART A



N,N-Dimethylethanolamine, N-methylmorpholine, and N-ethylmorpholine were treated with III to produce the respective ammonium and morpholinium salts (IV, V, VI). The synthesis of the new "phenolic invert soaps" and some intermediates is represented schematically as in Chart A.

EXPERIMENTAL

4-tt-Octylresorcinol (I) (4, 5, 8). A. One mole (112 g.) of diisobutylene (b.p. 101–103°) was added to 50 cc. of glacial acetic acid and the resulting solution was cooled below 15°. With constant stirring, 98 g. of sulfuric acid diluted by 50 cc. of glacial acetic acid was added slowly to the first solution. The temperature was maintained below 15° during the process. The resulting cooled mixture was added, while stirring, to a solution of one mole (110 g.) of resorcinol in 110 cc. of glacial acetic acid, the temperature being maintained below 15°. After the addition, the stirring was continued for two hours. A pink solution resulted, which was allowed to come slowly to room temperature and then to stand for about 24 hours at room temperature. The reaction mixture was poured into 500 cc. of cold water, and 40 g. of sodium hydroxide was added under cooling. The lower, deeply colored layer was separated, washed with sodium carbonate solution, then water, and finally dried in ether solution with calcium chloride. The ether was evaporated, and the oily residue was fractionally distilled *in vacuo*. The fraction distilling 200° to 225° at a pressure of about 20–24 mm. was collected. The distillate appeared as a yellow oil which crystallized to a white solid on standing; crude yield about 40%. On repeated recrystallization of the product from petroleum ether, long white crystalline needles, melting 106–108°, were obtained (5).

Anal. Calc'd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.98.

Found: C, 75.57; H, 10.11.

B. One mole (112 g.) of diisobutylene and one mole (110 g.) of resorcinol were well mixed with an efficient stirrer until a paste-like consistency was effected (4, 8). At this point, a few drops of concentrated sulfuric acid was added. The temperature rose spontaneously to about 70°, and the mixture became oily. An additional 3 g. of sulfuric acid was added and the mixture was stirred vigorously for about one to two hours, while the mixture cooled and set into a solid mass. After allowing the solid mass to stand for about 4 hours, it was broken up into small pieces, boiled and stirred with 1 liter of water to remove water-soluble impurities. The oily product was washed with hot water several times and then dried. On recrystallization from petroleum ether 4-*tt*-octylresorcinol was obtained in good yield (40 to 60%).

1-Benzoyl-4-tt-octylresorcinol (Ia). The preparation of the monobenzoate involved the Schotten-Baumann reaction in an aqueous sodium hydroxide medium (9). The 4-*tt*-octylresorcinol (I) (22 g., 0.1 mole) was suspended in 100 cc. of 10% aqueous sodium hydroxide solution. To this mixture was added, in small portions, with constant stirring, 14 g. (0.1 mole) of benzoyl chloride. The reaction mixture was warmed gently, with stirring, on a steam-bath and was then permitted to stand for about 30 minutes. The reaction product separated initially as an oil, but solidified after being washed with water and standing. The benzoate was purified in an ethereal solution, where it was washed with 5% aqueous sodium carbonate solution and water and dried. After removing the ether by distillation *in vacuo*, the oily residue was dissolved in a benzene-petroleum ether mixture, from which fine, white crystalline platelets of the benzoate, m.p. 170–171.5° were obtained on recrystallization.

Anal. Calc'd for $C_{21}H_{30}O_3$: C, 77.27; H, 8.03.

Found: C, 77.33; H, 8.24.

4-tt-Octylresorcinol dibenzoate (Ib). By treating 4-*tt*-octylresorcinol (I) (22 g., 0.1 mole) with 2 molar equivalents (28 g.) of benzoyl chloride in anhydrous pyridine (100 cc.) the dibenzoate was found to be the principal product (10, 11). The reactants were mixed and refluxed for 30 minutes. The reaction mixture was cooled and poured into 250 cc. of 2% aqueous sulfuric acid. The product precipitated as a white oil which solidified on standing. It was purified by solution in ether, where it was washed with 5% sodium carbonate solution and water, and dried with calcium chloride. On evaporation of the ether, the residual oil was crystallized from 95% alcohol. On recrystallization of the white crystalline platelets from the same solvent, the dibenzoate Ib, m.p. 146–147.5°, was isolated. By dilution of the 95% alcoholic mother liquor with water, some of the monobenzoate Ia was also obtained.

Anal. Calc'd for $C_{28}H_{40}O_4$: C, 78.11; H, 7.02.

Found: C, 78.31; H, 7.24.

4-tt-Octylresorcinol di-(p-nitrobenzoate) (Ic). 4-*tt*-Octylresorcinol (5.0 g., 0.022 mole) and *p*-nitrobenzoyl chloride (8.2 g., 0.044 mole) were condensed in 15 cc. of anhydrous pyridine in a manner described in the previous preparation (Ib). The crude product was worked up as described above, and was recrystallized from a mixture of ether (3 parts) and ethanol (1 part). The purified di-(*p*-nitrobenzoate) Ic appeared in the form of very light, greenish white crystals, m.p. 154–155.5°.

Anal. Calc'd for $C_{28}H_{28}N_2O_8$: C, 64.60; H, 5.42; N, 5.38.

Found: C, 64.59; H, 5.82; N, 5.60.

1-Benzoyl-6-nitro-4-tt-octylresorcinol (Id). With gentle heating 33 g. (0.1 mole) of 4-*tt*-octylresorcinol monobenzoate (Ia) was dissolved in 500 cc. of glacial acetic acid. After cooling the solution to about 30°, 30 cc. of a nitration mixture consisting of 43% aqueous nitric acid (*d* 1.2) was slowly added, with constant stirring, so that the temperature did not rise above 38–40° (9). When all the nitrating agent was added, yellow crystals of the reaction product began to separate from the solution. The reaction mixture was allowed to stand for 30 minutes, was cooled and filtered. The crystals were washed with water, and recrystallized from an acetic acid-water mixture, and finally from a small volume of 95% alcohol in the form of colorless, crystalline platelets, m.p. 202–203°.

Anal. Calc'd for $C_{21}H_{20}N_2O_6$: C, 67.88; H, 6.78; N, 3.77.

Found: C, 67.77; H, 7.00; N, 3.93.

1-Benzoyl-2,6-dinitro-4-tt-octylresorcinol (Ie). After filtering the mononitro compound Id from the reaction mixture in the above preparation, the clear filtrate was poured into a mixture of ice and water, which caused an orange oil to precipitate. The oil was dissolved in ether, where it was washed with water, dried with calcium chloride, and treated with Norit. On evaporation of the ether, a yellow crystalline compound was obtained by recrystallization of the residue from petroleum ether. The product (Ie) gave the correct analysis for the dinitro compound, m.p. 124–125°.

Anal. Calc'd for $C_{21}H_{18}N_2O_7$: C, 60.57; H, 5.81; N, 6.72.

Found: C, 60.78; H, 6.20; N, 6.95.

1-Benzoyl-6-bromo-4-tt-octylresorcinol (If). To a solution of 6.4 g. (0.02 mole) of 4-*tt*-octylresorcinol monobenzoate (Ia) in 50 cc. of glacial acetic acid was added 2 cc. of bromine diluted with 25 cc. of glacial acetic acid in small portions (9). The reaction mixture finally assumed a permanent red-orange color and was permitted to stand for 30 minutes after all of the brominating agent was added. It was poured into 10 times its volume of a dilute aqueous sodium bisulfite solution. The bromo compound separated as a white solid, and was filtered, washed with water, and dried. The dry material was recrystallized from a mixture of benzene (small volume) and petroleum ether (excess). The purified bromo compound (If) appeared in the form of white crystalline needles, m.p. 143–144.5°.

Anal. Calc'd for $C_{21}H_{18}BrO_3$: C, 62.22; H, 6.22; Br, 19.72.

Found: C, 61.94; H, 6.21; Br, 20.01.

6-Nitro-4-tt-octylresorcinol (Ig). Was prepared by the hydrolysis of 6-nitro-4-*tt*-octylresorcinol monobenzoate (Id). Ten grams (0.03 mole) of Id was dissolved in 250 cc. of 10% alcoholic potassium hydroxide solution and the resulting solution was refluxed for 2 hours. The alkaline solution was acidified with 10% hydrochloric acid solution and extracted with ether. The ethereal extracts were combined and washed with water, and dried with calcium chloride. On evaporation of the ether, the residual oil solidified on standing, and was recrystallized from petroleum ether in the form of a pale yellow-green crystalline powder, m.p. 142–143°.

Anal. Calc'd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.25.

Found: C, 62.71; H, 7.84; N, 5.30.

6-Chloro-4-tt-octylresorcinol (II). One mole (222 g.) of 4-*tt*-octylresorcinol (I) was dissolved in 1 liter of carbon tetrachloride and chlorinated with a chlorinating agent, consisting of 142 g. (1 mole + 5% excess) of sulfuryl chloride plus about 1.5 g. of sulfur chloride as a catalyst (12, 13, 14, 15). The chlorinating agent was added dropwise slowly to the carbon tetrachloride solution of I at an oil-bath temperature of 100–120°, after five grams of

aluminum chloride was added to the reaction mixture as an additional chlorine carrier. When all of the chlorinating agent was added, the time requiring about 1 hour, the reaction mixture was allowed to reflux an additional 2 hours. On cooling to room temperature, the reaction mixture was washed with water to remove all water soluble impurities. The carbon tetrachloride layer was separated, and to it was added an excess of ether. The resultant solution was dried with calcium chloride. The solvent was removed by distillation *in vacuo* and the residual, dark brown, oily product was purified by distillation at 2 to 4 mm. The fraction distilling at 140–160° (bath temperature, 190–210°) was collected. The distillate, a light yellow oil, solidified on standing to a white crystalline mass, yield about 50%. It was recrystallized from petroleum ether as white crystalline needles of 6-chloro-4-*tt*-octylresorcinol, m.p. 88–89°.

Anal. Calc'd for $C_{14}H_{21}ClO_2$: C, 65.48; H, 8.24; Cl, 13.81.

Found: C, 65.12; H, 7.92; Cl, 13.77.

*3-Benzoyl-6-chloro-4-*tt*-octylresorcinol (IIa)* 6-Chloro-4-*tt*-octylresorcinol monobenzoate (IIa) was prepared by treating 26 g. (0.1 mole) of 6-chloro-4-*tt*-octylresorcinol with 14 g. (0.1 mole) of benzoyl chloride in a 10% aqueous sodium hydroxide solution, as in the preparation of 4-*tt*-octylresorcinol monobenzoate (Ia). The purified material was recrystallized from a small volume of benzene plus an excess of petroleum ether. A white crystalline powder, m.p. 147–148.5°, was obtained.

Anal. Calc'd for $C_{21}H_{25}ClO_3$: C, 69.89; H, 6.98; Cl, 9.83.

Found: C, 69.93; H, 7.04; Cl, 9.54.

*Methylene bis-(6-chloro-4-*tt*-octylresorcinol), or (2,2',6,6'-tetrahydroxy-3,3'-dichloro-5,5'-di-*tt*-octyldiphenylmethane) (IIb)* Twenty-six grams (0.1 mole) of 6-chloro-4-*tt*-octylresorcinol (II) was dissolved in 50 cc of glacial acetic acid. To this solution was added 5 g. (0.05 mole + 5% excess) of formaldehyde solution (37%) To the resulting mixture was added 25 cc. of 15% aqueous hydrochloric acid. The reaction mixture was heated to a low boil for about 15 minutes and then allowed to cool. On pouring the mixture into water and ice, a red oil precipitated. The oil was dissolved in ether, washed with water, dried with calcium chloride, treated with Norit, and recrystallized from petroleum ether after evaporation of the ether. A white crystalline powder, melting 186–187.5°, was obtained. Microanalyses proved it to be the methylene bis derivative (IIb) of II.

Anal. Calc'd for $C_{22}H_{42}Cl_2O_4$: C, 66.27; H, 8.06; Cl, 13.49.

Found: C, 66.64; H, 8.15; Cl, 13.90.

*6-Chloro-4-*tt*-octyl-1-hydroxy-3-phenoxyethoxyethyl chloride (III)* One mole (257 g.) of 6-chloro-4-*tt*-octylresorcinol, four moles (562 g.) of β,β' -dichlorodiethyl ether, and one mole (42 g.) of 97% sodium hydroxide in 500 cc. of water, were placed in a large flask and heated under reflux at 100–120° for about 16 hours, under efficient stirring (6). At the end of the reaction period, the lower layer was separated, acidified and dissolved in ether. The ethereal solution was washed with water and dried with calcium chloride. On evaporation of the ether, the residual oily product was distilled at 4–5 mm. The main fraction distilled between 175–205°. The distillate appeared as a viscous, light yellow-orange oil, which produced crystals from petroleum ether. On recrystallization of the product from the same solvent, a white, crystalline powder, m.p. 87–88°, was isolated.

Anal. Calc'd for $C_{18}H_{28}Cl_2O_4$: C, 59.50; H, 7.77; Cl, 19.52.

Found: C, 59.75; H, 7.77; Cl, 20.10.

*N-[3-(6-Chloro-4-*tt*-octyl-1-hydroxy)phenoxyethoxyethyl]-N,N-dimethyl-N- β -hydroxyethyl ammonium chloride (IV)* A mixture of 36 g. (0.1 mole) of 6-chloro-4-*tt*-octyl-1-hydroxy-3-phenoxyethoxyethyl chloride (III) and 9 g. (0.1 mole) of dimethylethanamine were heated under reflux in an oil-bath at 160–180° for 6 hours (7). On cooling, the reaction mixture set into a stiff, purple-colored, water-soluble mass. The crude product was dissolved in absolute ethanol and treated with Norit several times. Upon removal of the solvent by distillation *in vacuo*, a viscous, light brown oil was obtained. The oily product was extremely soluble in water and its aqueous solution exhibited excellent surface active properties. Further purification of the product was effected by dissolving it in dry acetone

and precipitating it with an excess of petroleum ether. The solution and reprecipitation treatment was repeated several times. The supernatant liquid was decanted, and the oil was triturated with petroleum ether until it became a waxy solid. A small portion of the waxy solid was recrystallized from a mixture of dry acetone and petroleum ether on long standing. Long crystalline needles of the dimethylethanolamine salt (IV) were isolated and dried on a porous plate in a vacuum desiccator; m.p. 120–122°.

Anal. Calc'd for $C_{22}H_{29}Cl_2NO_4$: N, 3.10. Found: N, 3.35.

N-[5-(6-Chloro-4-*tt*-octyl-1-hydroxy)phenoxyethoxyethyl]-*N*-methylmorpholinium chloride (V). A mixture of 36 g. (0.1 mole) of 6-chloro-4-*tt*-octyl-1-hydroxy-3-phenoxyethoxyethyl chloride and 10 g. (0.1 mole) of *N*-methylmorpholine was refluxed in an oil-bath at 160–180° for 6 hours (7). The reaction product was cleaned by dissolving it in anhydrous alcohol and treating the resultant solution with Norit several times. The solvent was removed by distillation *in vacuo*. The residual, light brown, oily product was found to be very water-soluble and to exhibit excellent surface active properties in aqueous solutions. Further purification was achieved by dissolving the oil in dry acetone and precipitating it with an excess of petroleum ether. The solution and reprecipitation procedure was repeated several times. The purified oil was then dried in a high vacuum oven at 60°. A crystalline mass melting around 80–82° was obtained.

Anal. Calc'd for $C_{22}H_{29}Cl_2NO_4$: N, 3.07. Found: N, 3.17.

N-[5-(6-Chloro-4-*tt*-octyl-1-hydroxy)phenoxyethoxyethyl]-*N*-ethylmorpholinium chloride (VI). A mixture of 36 g. (0.1 mole) of 6-chloro-4-*tt*-octyl-1-hydroxy-3-phenoxyethoxyethyl chloride and 12 g. (0.1 mole) of *N*-ethylmorpholine was treated and worked up as described in the previous preparation. A crystalline mass melting around 83–85° was formed.

Anal. Calc'd for $C_{22}H_{41}Cl_2NO_4$: N, 2.92. Found: N, 2.55.

PHARMACOLOGICAL

Preliminary tests indicate that 4-*tt*-octylresorcinol and 6-chloro-4-*tt*-octylresorcinol are relatively non-toxic. Doses up to 1.0 gram of the drug were administered to dogs weighing 10 to 20 pounds without any noticeable gross toxic disturbances. Cows, weighing about 1200 pounds, were given doses as high as 30 grams a day for four days (120 grams) without any gross toxic symptoms being noted.

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SUMMARY

New phenolic compounds derived from 4-($\alpha,\alpha,\gamma,\gamma$ -tetramethyl)butyl-1,3-dihydroxybenzene, or 4-*tt*-octylresorcinol have been synthesized and characterized; these include, among others, 6-chloro-, 6-bromo-, 6-nitro-, 2,6-dinitro-, mono- and di-benzoyl-4-*tt*-octylresorcinols. One of the most outstanding of these compounds is the highly bactericidal and relatively non-toxic 6-chloro-4-*tt*-octylresorcinol, which was characterized with monobenzoyl and methylene-bis derivatives. A very significant fact was the discovery that the highly desirable antibacterial properties of the halogenated alkylresorcinol were found to be

carried over into a new series of ring-halogenated, phenolic, cationoidic, capillary-active and bactericidal quaternary ammonium salts derivatives, namely, 3-[6-chloro-4-($\alpha, \alpha, \gamma, \gamma$ -tetramethyl) butyl-1-hydroxy] phenoxyethoxyethyl substituted ammonium and morpholinium salts, where an intramolecular synchronization of desirable properties is effected. Bacteriological tests have shown these compounds to possess high phenol coefficients (100 to 200) against both gram-positive and gram-negative organisms.

NEW YORK, N. Y.

PEARL RIVER, N. Y.

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A STUDY OF REACTIONS OF GRIGNARD REAGENTS AT LOW TEMPERATURES¹

MELVIN S. NEWMAN AND ALLEN S. SMITH

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The effect of temperature on the course and extent of reactions involving Grignard reagents has rarely been studied below -30° . The outstanding example of a successful result at extremely low temperatures is the formation of acids by treatment of Grignard reagents with solid carbon dioxide (1). Recently it has been shown that at about -70° acetic anhydride reacts with various Grignard reagents to form the corresponding methyl ketones in high yield (2). In this paper we report on further studies of this reaction technique and demonstrate the reason for its success.

Effect of temperature. We have studied the reaction which takes place when a solution of butylmagnesium bromide is added to a solution of acetic anhydride in ether at different temperatures. It was found that from the reflux temperature of ether to about -40° the yield of ketone remained almost constant at 50%.² However, the yield increased rather sharply on further cooling and reached 79% near -70° . One experiment indicated that by going to lower temperatures higher yields might be obtained. However, because of the inconvenience we did not explore this region further. This temperature effect seemed to be about the same in the reaction of *t*-butylmagnesium chloride with acetic anhydride and of phenylmagnesium bromide with benzoic anhydride. At -70° each gave ketone in about 80% yield but at 0° the yields were about 50%. We did not investigate these cases further but assumed that they were approximately the same as for the case of *n*-butylmagnesium bromide and acetic anhydride. Our results are summarized in Table I.

The reactions were carried out in a special double-walled flask, shown in Figure 1. The *n*-butylmagnesium bromide was prepared and stored under pure dry nitrogen. The strength was determined by the acid titration method (4). Each run described in Table I involved the addition of 125 cc. of 2.03 *M* *n*-butylmagnesium bromide (0.257 mole) slowly over a period of two hours to a well-stirred solution of 55 g. (0.54 mole) of pure acetic anhydride in 125 cc. of dry ether. The temperature during the addition was recorded on a thermometer dipping into the liquid and was maintained at the desired point by a suitable cooling mixture or by the reflux of a suitable liquid in the outer jacket. After stirring for two hours after the addition was complete, the reaction mixture was allowed to come to -10° and then treated with a saturated solution of ammonium chloride. The ether layer was separated and washed with 5% sodium hydroxide to remove acetic anhydride and acetic acid and then with saturated sodium chloride. Any ketone in the washings was

¹ This material was taken from the Ph.D. thesis of Allen S. Smith, Ohio State University, June, 1947. Much of this work was presented before the Organic Division at the A.C.S. meeting in New York, September, 1947.

² Fournier (3) treated a series of primary halide Grignard reagents with a series of anhydrides at about -20° and reported yields in the range of 25-50%.

recovered by further ether extraction and added to the main batch. After filtration through anhydrous sodium sulfate the ether solution was treated in two ways to determine the amount of butyl methyl ketone: (a) titration of two 15-cc. aliquots (5); (b) isolation by careful fractionation of the remainder through a small packed column of about two plate

TABLE I
EFFECT OF TEMPERATURE ON YIELD OF 2-HEXANONE

REACTION TEMPERATURE °C	YIELD, % KETONE	METHOD OF ANALYSIS ^a	NUMBER OF EXPT'S
-82	83	t	1
-67	79	t, f	5
-54	64	t	2
-46	68	t	4
-37	51	t, f	3
-26	50	f	1
+ 5	48	t, f	2
+34 ^b	48	t, f	3

^a "t" indicates that the amount of ketone was determined by the titration method; "f" means the ketone was isolated by fractionation through a 6-inch column. The amount of ketone was considered to be the fraction boiling over a two-degree range around 126°, plus half of the material boiling in the region 100-125°. This usually amounted to an additional 5%.

^b No cooling bath was used.

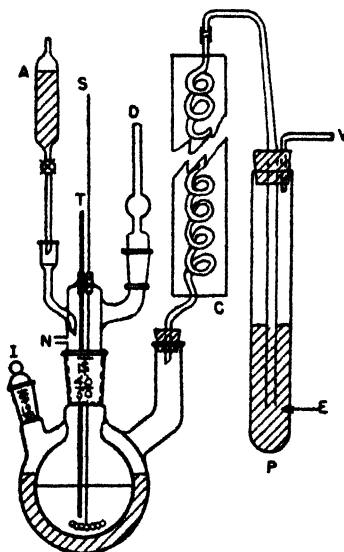


FIG. 1. DOUBLE WALLED FLASK

efficiency. After a number of runs showed that the values obtained by isolation ran uniformly 3 to 5% lower than the titration values, only the titration method was used. The butyl methyl ketone was characterized by its boiling point, 125-127°, and by the formation of its semicarbazone, m.p. and mixed m.p. 121-122° (6).

Effect of variations from standard technique. Our studies show that the use

of excess acetic anhydride does little to improve the yield and that a good commercial grade is about as satisfactory as redistilled anhydride. The concentration of the ethereal anhydride solution is relatively unimportant. The rates at which the Grignard reagent is added should not exceed one-third of a mole per hour for best results, but even with very rapid addition the yield of ketone is quite high. Precooling of the Grignard reagent is generally unnecessary. Rapid stirring during the addition period is important. Reversal of the order of addition, *e.g.*, adding anhydride to Grignard reagent, causes a large drop in yield. The results are summarized in Table II.

Effect of variation of Grignard reagent and anhydride. The preparation of ketones by this method seems to be quite general. Primary, secondary, tertiary, and aromatic Grignard reagents gave high yields when reacted with acetic,

TABLE II
EFFECT OF VARIATION FROM STANDARD TECHNIQUE ON YIELD OF KETONE

CONDITIONS ^a	YIELD IN % ^b
Standard (for Table I).	79
Equal molar amount of anhydride.	74
Equal molar amount of anhydride T = 30-34°.	39
Rapid addition, 0.3 moles in 50 minutes	75
Rapid addition, 0.1 moles in 2 minutes ^c	61
Commercial anhydride ^d	77
Less ether (25 cc. of ether to 55 g. of anhydride).	80
No nitrogen atmosphere.	67*
Anhydride added to Grignard reagent.	39*

* All conditions except those noted in this column were the same as those described as standard for Table I.

^b Yields are based on from two to five experiments except those yields marked with an asterisk (*) which were single runs.

^c The temperature rose to -60° during this addition.

^d Carbide and Carbon product.

propionic, and butyric anhydrides. With chloroacetic anhydride the yield fell to 35-50%, but this method appears at least comparable to other methods of preparing chloromethyl ketones using organometallic reagents (7, 8). It was rather surprising that good yields of keto acids could be obtained by using a cyclic anhydride in spite of the low solubility of these substances at low temperature. We did not investigate this phase to any great extent but did secure encouraging results. It would appear that this procedure will prove very useful in the preparation of certain β -aroylpropionic acids not directly obtainable by the Friedel-Crafts method. Our results are summarized in Table III.

Low temperature reactions with other compounds. We investigated the reaction of Grignard reagents with esters and acid chlorides but found little improvement over the corresponding reactions when carried out at room temperature. In these cases it is noteworthy that no insoluble complex separates during the reaction. This is significant for we believe that the nature of the insoluble complex

formed in the anhydride reaction accounts for the success of the low temperature technique. The arguments for this view are presented below.

We found that diisopropyl ketone and *n*-propylmagnesium bromide react at -70° to give addition and reduction products in the same ratio as found pre-

TABLE III
VARIATIONS IN ANHYDRIDE AND GRIGNARD REAGENT
 $(\text{RCO})_2\text{O} + \text{RMgX} \rightarrow \text{RCOR}' + \text{RCO}_2\text{MgX}$

R	R'	YIELD, % KETONE ^a
CH ₃	CH ₃ CH ₂ CHCH ₃	80 ^b , 75 ^c
CH ₃	(CH ₃) ₃ C	78 ^b , 74 ^c
CH ₃	C ₆ H ₅	75 ^b , 73 ^c
CH ₃ CH ₂	CH ₃ CH ₂ CH ₂ CH ₂	74 ^b
CH ₃ CH ₂ CH ₂	CH ₃ CH ₂ CH ₂ CH ₂	73 ^b
C ₆ H ₅	C ₆ H ₅	87 ^b , 75 ^d
ClCH ₂	CH ₃ CH ₂ CH ₂ CH ₂	35 to 50 ^{e,e}
Succinic anhyd.	C ₆ H ₅	50-70 ^f
Succinic anhyd.	<i>o</i> -CH ₃ C ₆ H ₄	35 ^g

^a Based on the Grignard reagent.

^b As determined by titration method, Bryant and Smith, *J. Am. Chem. Soc.*, **57**, 57 (1935).

^c Our methyl isobutyl ketone boiled at $116-119^{\circ}$ (Heilbron "Dictionary of Organic Compounds", Oxford University Press, New York, N. Y., 1943, Vol. II, pg. 639 gives 118°). Our pinacolone boiled at $104-106^{\circ}$ (Heilbron, Vol. III pg. 493 gives $103-106^{\circ}$). Our acetophenone, b.p. $198-202^{\circ}$, (Heilbron, Vol. I, pg. 15 gives 202°).

^d Isolated as the oxime m.p. $141-143^{\circ}$ (Heilbron, Vol. I, pg. 226, m.p. 144°). The solvent used for the anhydride in this reaction consisted of equal weights of ether and toluene.

^e The yield is particularly sensitive to experimental conditions. In these reactions the ethereal reaction mixture was washed with 5% sodium carbonate solution instead of sodium hydroxide. The product was isolated as a pink lachrymatory liquid, n_D^{20} 1.4400, b.p. $70-71^{\circ}$ at 15 mm., which darkened on standing. Verbanc and Hennion, *J. Am. Chem. Soc.*, **60**, 1711 (1938) give b.p. $73-74^{\circ}$ at 20 mm., n_D^{20} 1.4370.

^f The solvent for the anhydride was 80% ether and 20% pyridine (by weight). The Grignard reagent was added very slowly. The yield of crude acid, m.p. $95-110^{\circ}$ was 70%. Recrystallization from water gave the product m.p. $115-116^{\circ}$, neutral equivalent 181 (theory 178) in 50% yield.

^g The solvent for the anhydride was 60% pyridine, 40% ether, by weight. The reaction became very pasty; it was worked up by neutralizing with sodium carbonate after hydrolysis, and steam distilling the solvents. The crude acid obtained on acidification melted from 88 to 100° . Crystallization from water gave 35.2% of the theoretical amount of keto acid, m.p. $98-102^{\circ}$, neutral equivalent 190 (molecular weight 192). Analysis, calculated as C₁₁H₁₂O₃. Carbon, calculated 68.7%, found 68.7. Hydrogen, calculated 6.3%, found 6.4.

viously (9). In the case of 1:2 and 1:4 addition to α,β -unsaturated ketones, we found the same ratio in the case of ethylmagnesium bromide and benzalacetophenone at -70° as Kohler formed in the range -37 to 35° (10).

Of particular interest are our findings with regard to *m*-nitrobenzaldehyde. Ordinarily it is considered unwise to attempt to react Grignard reagents with

functional groups in compounds containing a nitro group because of the ready reaction of this group. We were able to isolate phenyl *m*-nitrophenyl carbinol in 77% yield (based on Grignard reagent) from the reaction at -70° of phenylmagnesium bromide with *m*-nitrobenzaldehyde. However, with butylmagnesium bromide only tarry products were obtained.

Grignard reactions with di-isopropyl ketone. A solution of 50 g. (0.44 mole) of di-isopropyl ketone in 50 cc. of ether was added dropwise over a period of two hours to 0.625 mole of *n*-propylmagnesium bromide in 500 cc. of ether at -70° . After 5 hours at -70° , the mixture was allowed to come to room temperature and stand for 10 hours. After hydrolysis with dilute sulfuric acid the product was distilled to yield two fractions: 34.5 g., b.p. $120-140^{\circ}$; and 16.2 g. (23%), b.p. near 100° at 50 mm. The higher-boiling fraction was taken as *n*-propyl di-isopropyl carbinol. By the usual ketone titration (5) the lower-boiling fraction was shown to contain 17 g. of ketone (calculated as starting ketone). Assuming the remainder to be di-isopropyl carbinol, the yield of reduction product was 34%. A similar reaction except that the temperature of reaction was 30° gave 18.5% of tertiary alcohol, 23% of unreacted ketone, and 39% of reduction product (9).

Grignard reactions with benzalacetone. In the usual apparatus 30 g. (0.205 mole) of benzalacetone in ether was added dropwise to 0.292 mole of ethylmagnesium bromide at -70° . After 12 hours an excess of alcohol was added and the reaction mixture hydrolyzed at room temperature with ammonium chloride. On distillation there was obtained 31 g. (81%) of a fraction b.p. $138-145^{\circ}$ at 25 mm. On treatment in acetone with potassium permanganate the unsaturated alcohol was destroyed (10). The remaining saturated ketone amounted to 17.5 g. (57% of the reaction products), b.p. 136° at 22 mm. In a similar reaction except that the Grignard reagent was added to the benzalacetone, the yield of mixed 1:2 and 1:4 addition products was less than 40% but the ratio was about the same. When this reaction was repeated at 30° , the same products in the same ratio were obtained.

Grignard reactions with m-nitrobenzaldehyde. An ether solution containing 0.196 mole of phenylmagnesium bromide (by titration) was added over a period of two hours to a solution of 47 g. (0.312 mole) of *m*-nitrobenzaldehyde in 650 cc. of toluene at -70° . After stirring for two hours more, an excess of alcohol was added (to decompose unreacted Grignard reagent) and the reaction mixture was treated with dilute hydrochloric acid. The carbinol distilled at $208-212^{\circ}/6$ mm. as a thick oil which crystallized, on long standing at 0° , and melted at $68-71^{\circ}$. A similar experiment at room temperature yielded only intractable tar.

Anal. Calc'd for $C_{13}H_{11}NO_2$: C, 68.1; H, 4.8; N, 6.1.

Found (on liquid): C, 68.3, 68.2; H, 5.0, 4.8; N, 6.2, 6.3.

The 3,5-dinitrobenzoate was prepared, and melted at $119.5-121.0^{\circ}$ on crystallization from alcohol.

Anal. Calc'd for $C_{20}H_{13}N_2O_6$: C, 56.8; H, 3.2; N, 9.9.

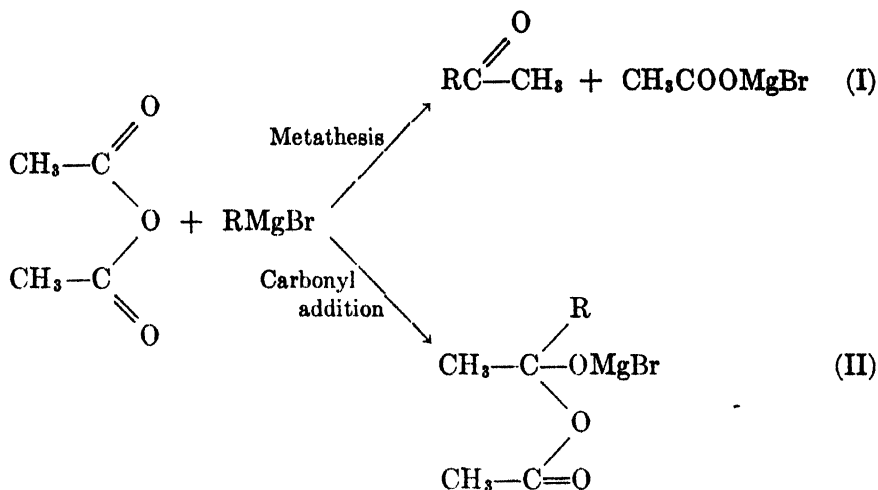
Found: C, 56.9, 56.8; H, 3.2, 3.6; N, 9.6, 9.5.

On oxidation at 60° with sodium dichromate (3 g.) and sulfuric acid in water the carbinol (2.5 g.) was converted into 1.5 g. of *m*-nitrobenzophenone (11) m.p. $93-95^{\circ}$.

Mechanism of the reaction between Grignard reagents and anhydrides. The mechanism of the reaction of Grignard reagents with acid anhydrides has not received much attention. Mechanisms for reactions between Grignard reagents and several acid derivatives have been discussed (12).

Two main courses are in general possible: The Grignard reagent may add to the carbonyl groups; or it may enter into a metathetical type reaction with some other linkage of the acid derivative (such as the chlorine in an acid chloride).

We have convincing evidence that with acetic anhydride at -70° the reaction follows the second path as shown below.



It was observed that when a solution of butylmagnesium bromide was added to a solution of acetic anhydride in ether at -70° a white precipitate began to form immediately and increased in amount all during the addition. This precipitate might have been (a) the bromomagnesium acetate formed in accordance with equation (I); (b) the addition product (R = butyl) shown in equation (II); (c) a complex formed between anhydride and Grignard reagent, such as $(\text{CH}_3\text{CO})_2\text{O} \cdot \text{C}_4\text{H}_9\text{MgBr}$; or (d) a complex formed between 2-hexanone and bromomagnesium acetate, $\text{C}_4\text{H}_9\text{COCH}_3 \cdot \text{CH}_3\text{COOMgBr}$. We found that the clear supernatant solution (which could be separated from the insoluble compound) contained only traces of ketone, either before or after treatment with dilute acid. This experiment rules out (a). When the insoluble complex was treated at -70° with an excess of alcohol, and the reaction mixture then treated with dilute acid, the ketone was formed in the usual high yield. This experiment rules out a complex such as (c) since such a complex would be decomposed by alcohol to yield butane and not ketone. In another experiment, the reaction mixture was allowed to come to room temperature from -70° . An insoluble complex was still present (undoubtedly $\text{CH}_3\text{COOMgBr}$) but now the entire amount of ketone was shown to be in the ether solution. Furthermore, if the solution at room temperature was cooled back to -70° , the entire amount of ketone still remained in the ether layer. These experiments prove that the original insoluble complex (at -70°) is thermally unstable and on cooling does not form again. If the original complex (at -70°) were (d) then on cooling the mixture from room temperature to -70° , the original complex should be regenerated and the ketone would not be in solution. The above facts are consistent with the hypothesis that the reaction follows the course indicated by equation (II). The insolubility and thermal stability of this complex at the low

temperatures involved are probably the reasons for the success of the low temperature technique.

We have made another observation which is quite interesting and may on occasion be of considerable importance in running competitive Grignard reactions. When an ethereal solution of 2-hexanone was stirred at -65° with excess of *n*-butylmagnesium bromide for thirty minutes, only about 20% had reacted whereas under similar conditions acetic anhydride reacted almost completely. Such a result is surprising in view of the relative reactivity of acid derivatives and ketones at ordinary temperatures (13).

SUMMARY

A study of the reaction of Grignard reagents with various compounds at low temperature is described. With anhydrides ketones are obtained in excellent yield, and the effect of temperature of reaction on yield of ketone is described in detail for the reaction of *n*-butylmagnesium bromide with acetic anhydride.

It is shown that *n*-butylmagnesium bromide adds to a carbonyl group of acetic anhydride at -70° . The stability and insolubility of this addition product account for the high yield of ketone obtained.

It is possible to react phenylmagnesium bromide, but not butylmagnesium bromide, with *m*-nitrobenzaldehyde at -70° but not at 0° to obtain *m*-nitrobenzohydrol in high yield.

COLUMBUS, OHIO

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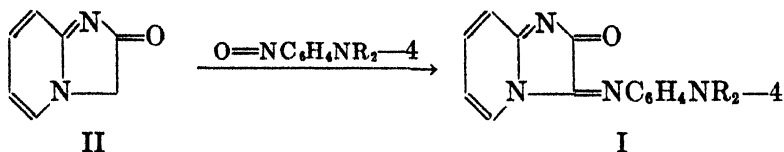
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CERTAIN AZOMETHINES IN THE 3a-AZAINDOL-2-ONE SERIES

C. F. H. ALLEN AND J. A. VANALLAN

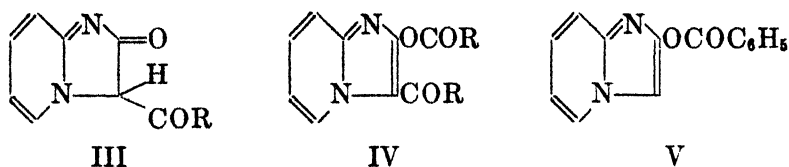
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The reaction between several 2-acylacetaminopyridines and certain aromatic nitrosoamines, which gave magenta-colored azomethine dyes (I) in the 3a-azaindol-2-one series,¹ was described in a previous paper. It was shown that the same product resulted from a given nitrosoamine and any of the 2-acylated aminopyridines, and that the substance was readily synthesized from the base (II) or its hydrochloride.



It was also shown that the magenta dyes gave bluish salts.

Analogous azomethines have been prepared from the 4-, 5-, and 6-methyl-2-aminopyridines. Of considerably more interest, however, is the observation that the mono- and di-acetylazaindolones (III, IV; R = CH₃) (3) give the same magenta dye as the unsubstituted heterocycle (II), the acetyl groups being eliminated in the process.



It was shown long ago (3, 4) that the O-acyl group in an azaindolone is extremely easily hydrolyzed off in alkaline solution—this would account for the loss of one acetyl group and formation of the monoacetylazaindolone from the diacetyl derivative. The remaining acetyl group then “couples out” during the reaction with the nitrosoamine; such an elimination of a group is known to occur in color photography.

3,3-Dibromo-3a-azaindol-2-one (5) likewise gives the same magenta dye with coupling out of the halogens. The simple acid salts, such as the hydrochloride, lose the acid when treated with sodium acetate and give the same magenta dye (1).

The important point is, that a given 3a-azaindolone, its simple salts, and its mono- or di-acyl derivatives, all give the same dye, and that dye has the structure shown in I.

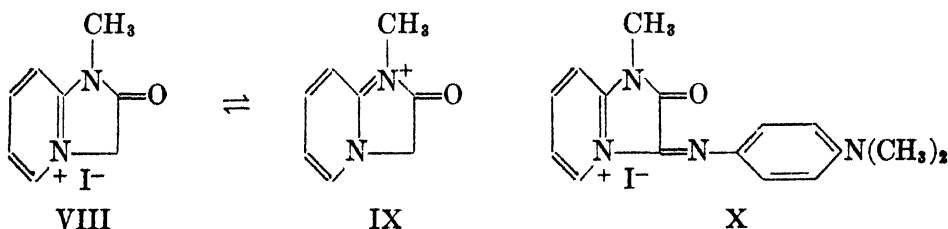
¹ In the previous paper (1) these substances were named as derivatives of pyrimidazole. However, the name pyrimidazole is not sufficiently specific, being used for several ring systems [Ring Index numbers 755, 756 and 765 (2)].

Other mono- and di-acyl derivatives would be expected to resemble the acetylated base. Thus, both O- (V) and C-benzoyl (III; $R = C_6H_5$) (3, 4) and distearoyl (IV; $R = C_{17}H_{35}$) (6) derivatives do not give dyes containing the acyl radicals, but the same magenta dye (I) already mentioned. The identity of the dye was determined by its isolation, observation of melting point, mixed melting point, and spectrophotometric data.² 3-Benzal-3a-azaindol-2-one likewise gives the same dye, but at a much slower rate.

From these facts it appears that the only variation that can be made in 3a-azaindolone couplers is to introduce substituents into the 6-membered ring (by use of substituted 2-aminopyridines) or to use benzologs (*e.g.*, 2-aminoquinolines).

The structures of 3a-azaindolone salts are difficult to represent by an unequivocal formula. As a monoacidic base, 3a-azaindol-2-one forms a monohydrochloride (7), a monohydriodide (7), and picrate (8), and a monomethiodide of the dye (I) has been reported (1).

We have found that 3a-azaindol-2-one (II) forms a monomethiodide and a perchlorate (VII). When the methiodide is treated with nitrosodimethylaniline, a bluish dye is formed; this substance appeared to be identical with the methiodide formed from the dye (I) ($R = CH_3$), and previously described (1). The structure ascribed earlier to this salt must therefore be in error; the methyl group must be on one of the heterocyclic nitrogen atoms. The methyl group is placed on the lactim nitrogen atom, which is in accordance with the ideas of Brooker (9); and also conforms with Chichibabin's hydriodide (VI) (8). The cation of the salt (VIII) so formed is one of several resonance forms, of which VIII is preferred since it contains an aromatic system. The methiodide of the dye is now assigned the structure shown in X.



EXPERIMENTAL

The 2-acetoacetamidopyridines were prepared as before (1); the 4-methyl derivative (XII) had the melting point 118–119°; the 5-methyl (XIII), 135°; and the 6-methyl (XIV), 98°. When these substances were treated with oxidized developer (unsymm.-diethyl-*p*-toluylenediamine), they gave yellow dyes which soon changed to magenta. The λ_{\max} for the magenta dye from XII is at 554; from XIII, at 564; and from XIV, at 560. The analyses are collected in Table I.

Diacetyl-3a-azaindol-2-one (XV) was obtained by refluxing a mixture of 5 g. of 3a-azaindol-2-one hydrochloride and 35 ml. of acetic anhydride until solution was complete; the yield, after cooling was 4.9 g.; m.p. 198°. Reindel and Rauch (3) started with pyridylglycine; the yield and melting point were the same. The distearoyl derivative (XI) was

² We are indebted to Dr. P. W. Vittum and Mr. G. H. Brown of these Laboratories for the last data.

prepared in a similar manner, using 11 g. of stearic anhydride per 1.4 g. of 3a-azaindol-2-one hydrochloride, and heating at 120° for one-half hour; at the end, the mixture was heated at 200° for ten minutes. After recrystallization from xylene, the yield was 3 g. The other 3a-azaindol-2-ones were obtained following the literature procedures.

The dye (I) was prepared from all the substituted 3a-azaindol-2-ones by the same general procedure (1). Equivalent amounts of *p*-nitrosodiethyl-*m*-toluidine, the heterocyclic substance, and a catalytic amount of potassium carbonate, in alcohol, were refluxed three to four hours. Usually, the dye separated in a reasonably pure condition; the yields were 50–60%. After recrystallization from butanol, the melting point was 203°; there was no depression on admixture with an authentic specimen (1). Spectrophotometric curves were also identical (2).

3a-Azaindol-2-one methiodide (VIII) was prepared from the hydrochloride as follows: 8 g. of the latter salt, 4.3 g. of sodium acetate, and 40 ml. of absolute ethanol were heated to boiling, treated with 3 g. of Norit, and filtered. To the red filtrate was added 40 ml. of methyl iodide and the solution left overnight in a closed bottle; 6.2 g. of bright red crystals separated. Even after recrystallization from ethanol, the product, m.p. 168–170°, was not

TABLE I
ANALYSES

NO.	SUBSTANCE	EMPIRICAL FORMULA	ANALYSES	
			Calc'd %, N	Found %, N
XII	4-Methyl amide	$C_{10}H_{12}N_2O_2$	14.6	14.4
XIII	5-Methyl amide	$C_{10}H_{12}N_2O_2$	14.6	14.4
XIV	6-Methyl amide	$C_{10}H_{12}N_2O_2$	14.6	14.7
XI	Distearoyl derivative	$C_{44}H_{74}N_2O_8$	4.2	4.3
VII	Perchlorate	$C_8H_9ClN_2O_8$	11.3	11.2
X	Dye	$C_{16}H_{17}IN_4O$	13.8	14.0
XVII	Dye perchlorate	$C_{16}H_{17}ClN_4O_8$	14.7	14.6

analytically pure, so it was transformed into the *perchlorate* (VII), m.p. 174–175°, by mixing 1.3 g. in 5 ml. of water with a warm solution of 1 g. of sodium perchlorate in an equal volume of water.

The methiodide (X) of the dye (I) was obtained by warming for three hours a mixture of 2.7 g. of 3a-azaindol-2-one methiodide, 1.4 g. of *p*-nitrosodimethylaniline, and 40 ml. of absolute ethanol. The yield was 3.7 g., 91%. It may be recrystallized from water, but a better product results if it is precipitated from its solution in nitrobenzene by ether; the melting point, 236–237°, is not depressed³ on admixture with an authentic specimen prepared in the earlier work (1). This dye was likewise converted into a *perchlorate* (XVII), m.p. 230°; it deflagrates like most perchlorates.

The dye base (I) gives a yellow solution in concentrated sulfuric acid.

When an alkaline solution of the dye or its methiodide (X) is boiled, an odor of an isocyanide is noticed and the deep bluish-red color changes to a dirty purple.

³ The melting point of the original sample was 240°; the mixed melting point with the 237–238° specimen was 238–239°, from which it may be concluded that the methiodides are identical. However, the behavior of the aqueous solution, on making alkaline with a few drops of sodium carbonate solution, is somewhat different. The difference is detected by shaking the straw-colored alkaline solution with butyl acetate. The specimen, m.p. 240°, gives a yellowish-orange ester layer, while the lower-melting isomer gives a magenta layer.

SUMMARY

The same azomethine dye, a derivative of 3a-azaindol-2-one, results when a variety of 3a-azaindol-2-ones, substituted in the 5-membered ring, are treated with aromatic nitrosoamines. Isomeric dyes are formed with alkyl groups in the 6-membered ring. Two methiodides and perchlorates are described and a type structure for such salts is proposed.

ROCHESTER 4, NEW YORK

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3-CARBOXYMETHYLBENZOTHAZOLINES

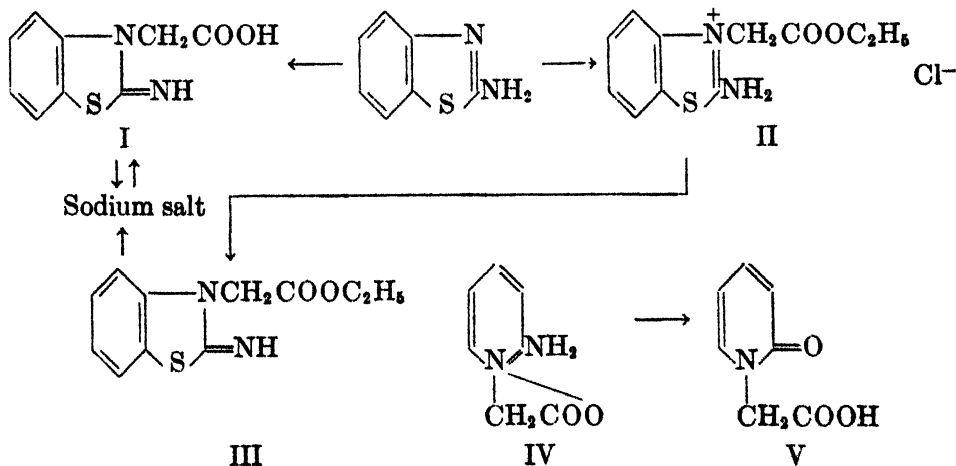
C. F. H. ALLEN AND J. A. VANALLAN

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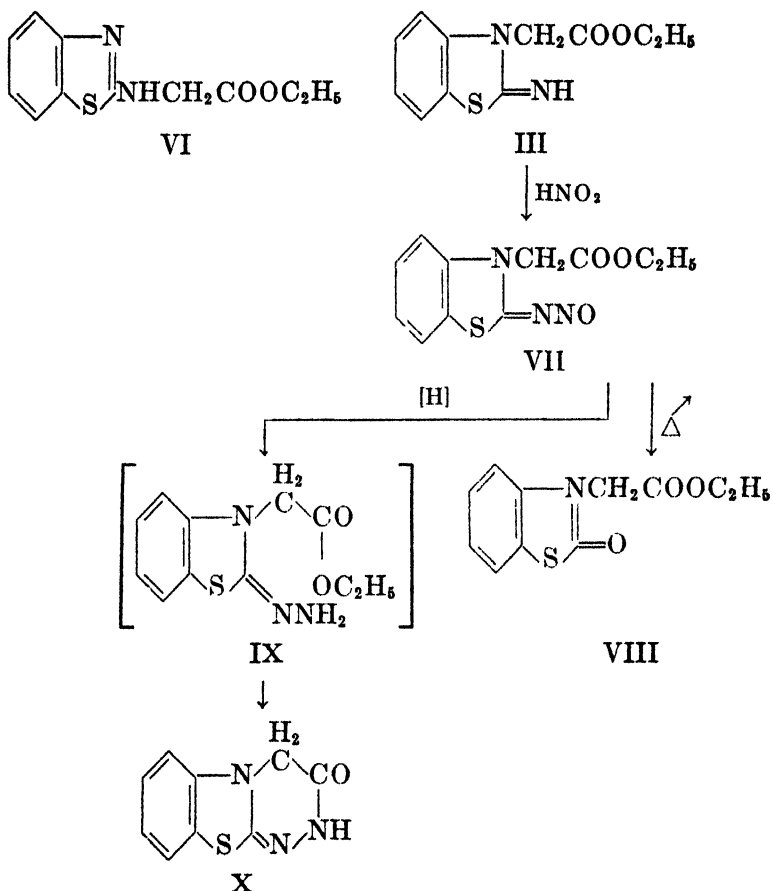
In an earlier paper (1) the failure of 2-acetoacetaminobenzothiazole to cyclize was mentioned, and this behavior was contrasted with the heterolog in the pyridine series. Attention was subsequently turned to the simpler system that resulted from the addition of chloroacetic acid to 2-aminobenzothiazole, which was expected to be comparable to the 2-aminopyridine heterolog. This present paper contains observations on the reactions of 2-aminobenzothiazole with chloroacetic acid, its sodium salt, and its ethyl ester.

In aqueous or acetic acid solution, equivalent amounts of 2-aminobenzothiazole and chloroacetic acid form a salt, from which the base can be recovered by making a solution of the salt alkaline and extracting with ether. Sodium chloroacetate in aqueous solution, however, adds to the heterocyclic nitrogen atom, to give, after acidification, 3-carboxymethyl-2-iminobenzothiazoline (I).

Ethyl chloroacetate gives an addition product (II) from which the free ester (III) is obtained by the action of sodium carbonate or dilute sodium hydroxide. When this ester is treated with hot sodium hydroxide solution, it is saponified and the sodium salt of (I) separates. In contrast to the behavior of 2-aminopyridylglycine (IV), which (a) crystallizes from dilute alkali unchanged, (b) evolves ammonia, on boiling with sodium hydroxide, to give N-carboxymethyl-2-pyridone (V), and (c) gives (V), on treatment with nitrous acid; 3-carboethoxymethyl-2-iminobenzothiazoline gives (a) the sodium salt of the acid on crystallization from dilute alkali, (b) does not evolve ammonia on boiling with caustic, and (c) gives a nitrosoamine on treatment with nitrous acid. On the basis of these facts, 3-carboxymethyl-2-iminobenzothiazoline is assigned an open-chain structure, whereas pyridylglycine has been assigned a betaine structure (2).

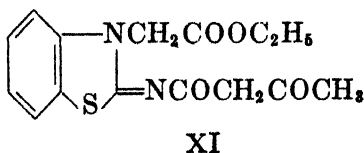


The ester formed from ethyl chloroacetate might have one of two structures, (III) or (VI). The evidence that favors (III) and excludes (VI) lies in its behavior with nitrous acid. With this reagent, a nitrosoamine (VII) is formed; when the latter is heated, nitrogen is evolved and the thiazolone (VIII) results. This behavior is characteristic of iminobenzothiazolines (3).



Reduction of the nitrosoamine, which would be expected to give the hydrazone (IX), gives a substance, the analysis of which shows that a molecule of alcohol has been lost; the tricyclic structure (X) is provisionally suggested for this product.

The imino-ester (III) gives an imide (XI) when treated with ethyl acetoacetate; attempts to cyclize this substance to a 7-membered ring were unsuccessful, the only reaction observed being hydrolysis of the ester to the free acid.



In the earlier paper (1), the failure of 2-acetoacetaminobenzothiazole to cyclize,

under conditions which resulted in ring closure with other heterocyclic acetoacetamides, was attributed to the inherent difficulty in forming the ring system composed of two fused 5-membered rings, attached, linearly, to a benzene nucleus. Subsequently, it has been claimed (4) that such a ring system is formed when 2-methylbenzobenzothiazole is treated with ethylene bromide. Now, in view of the well-known fact that alkylene halides in general give *bis*-quaternary salts with heterocyclic bases (5-10), it appears more likely that the substance mentioned in the patent (4) is, in reality, a "double-ender" salt.

As a test case, a substance described in example 1 of the patent was prepared from 2-methylbenzothiazole and trimethylene bromide.¹ This would form a 6-membered ring, and, thus, be the most favorable case to test. While the analytical figures for per cent of bromine do not distinguish between the two possibilities, the values for carbon differ by three per cent. The value, 45.0%, found for carbon agrees reasonably well with that calculated for the *bis*-salt (45.6%), and not with that calculated for a tricyclic ring system (48.8%). Consequently, it seems highly probable that all substances so obtained are *bis*-quaternary salts and not a 6,5,5-tricyclic system.

EXPERIMENTAL

*2-Aminobenzothiazole chloroacetate*² crystallized when a hot (90°), clear solution of 3.7 g. of 2-aminobenzothiazole, 2.4 g. of chloroacetic acid, and 40 ml. of water was cooled. The yield was 5.5 g. (92%). The salt retains solvent of crystallization tenaciously; it melts at 119-120°, with previous sintering after recrystallization from water and drying in a current of warm air. Acetic acid is also a suitable solvent for the reaction.

Anal. Calc'd for $C_8H_7ClN_2O_2S$: C, 44.2; H, 3.7; N, 11.4.

Found: C, 44.2; H, 3.4; N, 11.5.

The free base is liberated upon treatment with potassium carbonate or sodium acetate.

3-Carboxymethyl-2-iminobenzothiazoline (I). A solution of 15 g. of 2-aminobenzothiazole in 50 ml. of alcohol was added to the sodium chloroacetate prepared by mixing 9.4 g. of chloroacetic acid, 5.3 g. of sodium carbonate, and 10 ml. of water. The clear solution was heated on the steam-bath for 24 hours, the alcohol removed *in vacuo*, and 80 ml. of water added. The crude product was filtered, taken up in 3% ammonium hydroxide, treated with Norit, filtered, and acidified. On chilling, the acid crystallized. The analytical sample was recrystallized from acetic acid; it melted at 258°.

Anal. Calc'd for $C_8H_8N_2O_3S$: N, 13.5. Found: N, 13.2.

The sodium salt of this acid separated in shimmering plates, on chilling a hot solution made up from 2 g. of the acid, 30 ml. of water, and 5.6 g. of a 40% sodium hydroxide solution.

Anal. Calc'd for $C_8H_7N_2NaO_3S$: S, 13.9. Found: S, 14.1.

2-Amino-3-carboethoxymethylbenzothiazolium chloride (II) separates from a mixture of 15 g. of 2-aminobenzothiazole, 10.6 g. of ethyl chloroacetate, and 30 ml. of alcohol, after 15 hours' refluxing. The yield was 20 g. (74%). After recrystallization from ethanol, the melting point was 240-242°.

¹ This was selected instead of the benzobenzothiazole because the percentage compositions of the two products that could result from this heterocycle are too close to enable one to distinguish the two possibilities.

² We are pleased to acknowledge the assistance of Dr. J. H. Clark, Mr. C. O. Edens, and Miss E. R. Webster, who are responsible for the work in which acetic acid was used as a solvent, for the regeneration of the base, and for the preparation of analytical samples.

Anal. Calc'd for $C_{11}H_{13}ClN_2O_2S$: C, 48.5; H, 4.8; N, 10.3.

Found: C, 48.6; H, 4.5; N, 10.2.

The free base (III) is obtained by adding a hot sodium carbonate solution to a hot aqueous solution of the chloride; the yield was 10 g. (85%); the melting point was 122–123° after recrystallization from ethanol.

Anal. Calc'd for $C_{11}H_{13}N_2O_2S$: N, 11.9. Found: N, 12.0.

3-Carboethoxymethyl-2-nitrosiminobenzothiazoline (VII). To a solution of 7.2 g. of the base (III) in 40 ml. of acetic acid at room temperature was gradually added 3 g. of sodium nitrite in 16 ml. of water. The yellow solid that separated in a yield of 7.5 g. was crystallized from ethyl acetate; it melts at 148–149°, with decomposition.

Anal. Calc'd for $C_{11}H_{11}N_2O_3S$: N, 15.8; S, 12.1.

Found: N, 15.8; S, 11.8.

3-Carboethoxybenzothiazolone (VIII) was obtained by refluxing a solution of 4 g. of the nitroso derivative (VII) in 20 ml. of xylene for 1.5 hours; there was considerable foaming as the nitrogen was evolved. Most of the solvent was distilled, whereupon the thiazolone crystallized. It separated from ligroin (b.p. 90–120°) in long white needles; m.p. 96°.

Anal. Calc'd for $C_{11}H_{11}NO_2S$: S, 13.50. Found: S, 13.53.

3-Acetoacetimino-3-carboethoxymethylbenzothiazoline (XI) was prepared by the usual procedure (11) from a mixture of 7 g. of ethyl acetoacetate, 11.8 g. of the imino-ester (III), and 40 ml. of xylene; the solid that separated, when the solution was chilled, was recrystallized from benzene. The yield of product, m.p. 128°, was 12.3 g. (77%).

Anal. Calc'd for $C_{16}H_{18}N_2O_4S$: C, 56.2; H, 5.0.

Found: C, 56.1; H, 5.0.

The sodium salt of the acid resulted when 6 g. of the ester was refluxed for 2 hours with sodium ethoxide (made from 50 ml. of absolute methanol and 0.3 g. of sodium). The free acid was obtained by acidifying an aqueous solution of the salt; it melts at 168° after recrystallization from water.

Anal. Calc'd for $C_{13}H_{13}N_2O_4S$: C, 53.4; H, 4.1.

Found: C, 53.7; H, 3.9.

3-Keto-3,4-dihydro-2H,1,2,4a-triaza-9-thiafluorene (X). To a well-stirred mixture of 10 g. of the nitroso compound, 50 ml. of acetic acid, and 50 ml. of water, 20 g. of zinc dust was added in portions, the temperature being kept below 15°. After 1 hour, 10 ml. more of acetic acid was added, and the temperature allowed to rise to 21°, whereupon the suspension was decolorized. After the excess zinc was filtered, the filtrate was made alkaline with ammonium hydroxide, and the base was filtered; the yield was 8.4 g. After recrystallization from alcohol, the melting point was 260°.

Anal. Calc'd for $C_{11}H_{13}N_3O_2S$: N, 20.5. Found: N, 20.4.

Trimethylene-bis-2-methylbenzothiazolium bromide was prepared as directed (4); it melted at 254–256°, with decomposition.

Anal. Calc'd for a bis-salt, $C_{19}H_{20}Br_2N_2S_2$: C, 45.6; H, 4.0.

Calc'd for 3-ring substance, $C_{11}H_{13}BrNS$: C, 48.8; H, 4.5.

Found: C, 45.0; H, 3.9.

SUMMARY

2-Aminobenzothiazole forms a simple salt with chloroacetic acid, but sodium and ethyl chloroacetates give addition products from which 3-carboxymethylbenzothiazolines and 3-carboethoxymethylbenzothiazolines are easily obtainable. The behavior of these substances is contrasted with that of aminopyridylglycine. Other related compounds are described.

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AMINO CARBINOLS DERIVED FROM 2-ACETYLFLUORENE¹

LEWIS J. SARGENT AND LYNDON SMALL

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The marked plasmodicidal activity exhibited by amino carbinols of the type $>\text{CHOHCH}_2\text{NR}_2$ prepared from various acetylphenanthrenes (1) and 1-acetylnaphthalene (2) prompted this investigation, the objective of which was to synthesize and examine pharmacologically, analogous compounds derived from 2-acetylfluorene.

The proposed scheme called for the conversion of the ketone to the ω -bromo ketone, condensation of the latter with various secondary amines, followed by reduction of the resulting amino ketones to the amino carbinols, either catalytically (PtO_2) or with aluminum isopropoxide. In the initial bromination experiments, treatment of 2-acetylfluorene (3) in dry CHCl_3 (at 0°) afforded 2- ω -bromoacetylfluorene in 42% yield. In addition, some halogen-containing by-product was isolated which probably consisted of nuclear brominated material. It is known that bromination of fluorene in CHCl_3 solution leads to nuclear halogenation (4). Because of the tedious fractional crystallizations involved in the separation of the pure bromo ketone, an attempt was made to circumvent the bromination step through direct bromoacetylation of fluorene. The reaction of fluorene with bromoacetyl bromide in dry CS_2 (at -5°) in the presence of anhydrous AlCl_3 led to the desired 2- ω -bromoacetylfluorene (50% yield), identical with that obtained by brominating 2-acetylfluorene. The oily by-products of this reaction were not examined. The bromination of 2-acetylfluorene to the ω -bromo ketone, in anhydrous ether, in yields somewhat superior to those reported in this communication, was reported recently by Ray and MacGregor (5).

The bromo ketone-amine condensations were effected at room temperature either in ether, compounds 2, 4, 5, 7, 8 (Table I) or in chloroform, compound 3. In view of the relative instability of the free amino ketones it was found judicious, in all cases, to reduce these substances or their salts to the corresponding amino alcohols without delay. The amino ketones derived from the aliphatic amines were amber syrups, while those formed from the heterocyclic amines were crystalline. Owing, probably, to low basicity, the condensation of 1,2,3,4-tetrahydroquinoline with ω -bromoacetylfluorene could not be effected in solution. Fusion of the components at 100° , however, gave the desired (solid) amino ketone, but the latter could not be reduced to the corresponding amino alcohol. This abnormal behavior, towards hydrogen, of amino ketones derived from

¹ This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the National Institute of Health. The Survey Numbers correspond to those given in Wiselogle, "Survey of Antimalarial Drugs, 1941-1945", J. W. Edwards, Ann Arbor, 1946.

TABLE I
FLUORENE AMINO CARBINOLS

S.N.	COMPOUND	APPEARANCE	FORMULA	M.P., C.	ANALYSES			
					Calc'd		Found	
					C	H	C	H
—	2- ω -Bromoacetylfluorene	Prisms ^a	C ₁₆ H ₁₁ BrO	147-149	62.7	3.86	62.5	4.00
1807	2-(2-Diethylamino-1-hydroxyethyl)-fluorene HCl	Needles ^d	C ₁₉ H ₂₄ ClNO	172-174	71.8	7.61	71.9	7.71
15,077	2-(2-Di- <i>n</i> -propylamino-1-hydroxyethyl)-fluorene HCl	Prisms ^e	C ₂₁ H ₂₉ ClNO	175-177	72.9	8.16	72.7	8.19
1808	2-(2-Piperidino-1-hydroxyethyl)fluorene HCl	Plates ^e	C ₂₀ H ₂₄ ClNO	256-257d.	72.8	7.33	72.5	6.88
1811	2-(2-Morpholino-1-hydroxyethyl)fluorene HCl	Long Plates ^b	C ₁₉ H ₂₃ ClNO ₂	246-247d.	68.7	6.68	68.7	6.55
2695	2-(2-Tetrahydroquinolino-1-oxoethyl)-fluorene	Leaves ^f	C ₂₁ H ₂₁ NO	166-168	84.9	6.24	84.5	6.63
1809	2-(2-Tetrahydroisoquinolino-1-hydroxyethyl)fluorene HCl ^g	Plates ^d	C ₂₃ H ₂₄ ClNO	248-249d.	76.2	6.40	75.8	6.38
—	2-(2- <i>trans</i> -Decahydroquinolino-1-oxoethyl)fluorene ^h	Crusts ^e	C ₂₃ H ₂₇ NO	104-106	83.4	7.88	82.8	8.04
1810	2-(2- <i>trans</i> -Decahydroquinolino-1-hydroxyethyl)fluorene HCl	Needles ^b	C ₂₄ H ₂₉ ClNO	263-264d.	75.0	7.88	74.7	8.21

^a Acetone. ^b Absol. alcohol plus ether. ^c Methanol. ^d Methanol plus ether. ^e Acetone, methanol plus ether. ^f Absol. alcohol.^g Acetone.

ω -bromomethyl ketones with tetrahydroquinoline has been observed by others in this Laboratory in the naphthalene (6) as well as in the phenanthrene series (1).

The synthesis of 2-(2-diethylamino-1-hydroxyethyl)fluorene hydrochloride outlined below, is illustrative of the methods used in the preparation of compounds 2, 4, 5, 7, 8 (Table I). With compounds 4 to 8, however, the solid amino ketones were usually mixed with amine hydrobromides. Separation of the two was readily effected by repeated leachings with warm (60°) water in which the amine hydrobromides were soluble. The insoluble amino ketones were then purified either alone or as their hydrochlorides and then reduced. The synthesis of 2-(2-di-*n*-propylamino-1-hydroxyethyl)fluorene hydrochloride, compound 3, describes the aluminum isopropoxide reduction of the amino ketone to the amino carbinol.

Plasmodicidal activity towards *P. gallinaccum* (chick infection) was absent in the amino carbinols described in this work.

ACKNOWLEDGMENT

The microanalyses are by E. A. Garlock, Jr., formerly of this Laboratory.

EXPERIMENTAL

Melting points are uncorrected.

2- ω -Bromoacetylfluorene by bromination of 2-acetylfluorene. To a cooled (0°) and stirred solution of 8 g. of 2-acetylfluorene (3) in 75 ml. of C.P. CHCl_3 , containing a few drops of a solution of HBr in glacial acetic acid, 6.15 g. (1 mole) of bromine was added dropwise during 1 hr. After stirring at 0° and at room temperature respectively for 0.25-hr. periods, a quantity of yellow, crystalline, CHCl_3 -insoluble material was removed and the filtrate concentrated to a syrup *in vacuo*. On cooling, the latter afforded 5.7 g. of crude, crystalline material which consisted of the bromo ketone mixed with nuclear-halogenated material. Recrystallization from acetone (Norit) gave 2.7 g. of bromo ketone, m.p. 143–145°. The concentrated mother liquor yielded another 0.7 g.

The chloroform-insoluble fraction, probably a perbromide, was dissolved in boiling CHCl_3 (attended by copious HBr evolution) and the solvent removed *in vacuo*. The residual, syrupy product was dissolved in acetone (Norit), concentrated, seeded with the above bromo ketone and refrigerated for 24 hrs. This afforded a further quantity (1.3 g.) of bromo ketone of m.p. 140–143°, (total yield 4.7 g. or 42%). 2- ω -Bromoacetylfluorene crystallizes in slender, colorless prisms from acetone, m.p. 147–149° (after 3 recrystallizations).

2- ω -Bromoacetylfluorene by direct bromoacetylation of fluorene. A stirred solution of 50 g. of fluorene in 350 ml. of dry CS_2 was cooled to –5° and treated all at once with 88 g. (2.2 moles) of powdered, anhydrous AlCl_3 . The color of the solution darkened to a brownish-purple and the temperature rose slightly. During the course of 0.75 hr., a solution of 65 g. (1.05 moles) of bromoacetyl bromide in 45 ml. of CS_2 was added dropwise while the temperature was held at ca. –4°. Stirring was continued at –4° to 0° for 3 hrs., then for another 2.5 hrs. at 0° to +5°. The reaction mixture was poured onto a mixture of cracked ice and 2 *N* HCl, a little ether was added to take up a small amount of oily by-product, and the suspension shaken vigorously for several minutes to complete decomposition of the reaction product. The resulting, cream-colored suspension was refrigerated overnight, filtered, washed with water and dried; yield 80 g. Recrystallization from acetone (Norit) afforded 36.5 g. of pure 2- ω -bromoacetylfluorene identical with that obtained above. From the concentrated mother liquor, another 7 g. of bromo ketone was isolated (total yield, 43.5 g. or 50%).

2-(2-Diethylamino-1-oxoethyl)fluorene hydrochloride. A mixture of 12 g. of 2- ω -bromoacetylfluorene with 6.75 g. (2.2 moles) of diethylamine in 200 ml. of ether was shaken for 12 hrs. After removing the precipitated diethylamine hydrobromide (6 g., 93%), the ethereal solution of the amino ketone was washed several times with cold water and dried over sodium sulfate. The filtered solution was cooled in ice, treated with one-third of the calculated amount of 6 *N* alcoholic HCl and seeded with crystals obtained in a test tube experiment. After 10 mins., the remaining two-thirds of alcoholic HCl was added and the whole refrigerated for 12 hrs. The amino ketone hydrochloride was a pale-yellow, microcrystalline powder (11.5 g.), which was recrystallized by dissolving it in a mixture of acetone-ethanol (9:1) and diluting with dry ether; yield 8.7 g.

2-(2-Diethylamino-1-hydroxyethyl)fluorene hydrochloride. Reduction of the above described amino ketone hydrochloride (8.7 g.) in absolute methanol solution (125 ml.), in the presence of PtO₂ (0.2 g.), proceeded smoothly and was complete in 8.5 hrs. The syrup obtained from the filtered and concentrated (*vacuo*) solution was taken up in the minimum of acetone and refrigerated for 36 hrs. During this interval 5.8 g. (65%) of colorless crystals separated. The salt crystallized in rosettes of colorless needles from an absolute ethanol-ether mixture, m.p. 172-174°.

2-(2-Tetrahydroquinolino-1-oxoethyl)fluorene. Five grams of 2- ω -bromoacetylfluorene was covered with 4.8 g. (2 moles) of tetrahydroquinoline² and the mixture heated at 95-100° (oil-bath) for 10 mins. On cooling, the melt solidified to a hard, yellow-brown cake, which was broken up and digested several times with hot water in order to remove the amine hydrobromide. The pale-yellow, insoluble material was filtered and dried; 6 g. From dilute acetone (Norit), the amino ketone crystallized in pale yellow plates, m.p. 167-169°. This substance could not be hydrogenated to the corresponding carbinol under the conditions employed for the reduction of the other amino ketones in this series.

*2-(2-Di-*n*-propylamino-1-hydroxyethyl)fluorene hydrochloride.* To a solution of 12 g. of 2- ω -bromoacetylfluorene in 100 ml. of C.P. CHCl₃ was added 8.4 g. (2 moles) of di-*n*-propylamine and the mixture kept at 20° overnight. Concentration of the solution at 40-45° (*vacuo*) afforded a syrup which was triturated with 80 ml. of dry ether and cooled in ice, whereupon 6.9 g. (92%) of amine hydrobromide was recovered. The oily amino ketone (13.3 g.) obtained from the concentrated filtrate was reduced by the method of Meerwein, Ponndorf, and Verley employing 48 ml. (1.1 moles) of 3 *N* aluminum isopropoxide solution. The resulting, syrupy amino alcohol solidified to a waxy mass on standing overnight. Preparation of the hydrochloride was effected in absolute ethanol solution using a slight excess of 20% alcoholic HCl; addition of dry ether (to light turbidity) caused the slow separation of a light tan, microcrystalline powder (6.3 g.). Three recrystallizations from a concentrated acetone solution (Norit) afforded minute, colorless prisms, m.p. 173-175°.

SUMMARY

The synthesis of 2- ω -bromoacetylfluorene by (a) bromination of 2-acetylfluorene and (b) bromoacetylation of fluorene is reported.

The preparation of a series of amino carbinols derived from 2-acetylfluorene is described.

Plasmodicidal activity was absent in this group of compounds.

BETHESDA 14, Md.

² 1,2,3,4-Tetrahydroquinoline was prepared by high-pressure reduction (copper-chromite) of quinoline. For the preparation of 1,2,3,4-tetrahydroisoquinoline and *trans*-decahydroquinoline, see ref. 7 (a) and (b) respectively.

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5,6-DIACETYL-L-ASCORBIC ACID

MARTHA CREIGHTON, WILHELM WENNER, AND H. M. WUEST¹

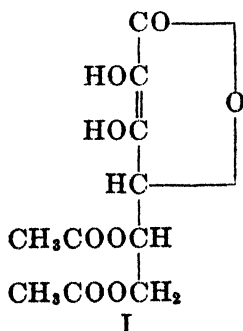
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Soon after its isolation, L-ascorbic acid was shown to be related to sugars, and during determination of its structure the usual reactions in sugar chemistry were studied. One of the most useful of those reactions is acetylation. Converting the reactive free hydroxyl groups into acetoxyl groups allows degradation studies impossible with the free sugars.

Consequently Svrbely and Szent-György tried to obtain an acetyl derivative of L-ascorbic acid (2). They were not able to isolate a crystalline acetyl derivative. Ohle (1) likewise could not prepare crystalline acetyl derivatives of D-isoscorbic acid. It seems that other attempts to acetylate L-ascorbic acid also were unsuccessful since the extensive literature on L-ascorbic acid published within the last fifteen years fails to mention an acetyl derivative. That efforts to acetylate L-ascorbic acid were never abandoned is evident from a paper published by Vestling and Rebstock in 1944 (3), where the authors report the preparation of 3-acetyl-5,6-isopropylidene-L-ascorbic acid.

Several years ago we reinvestigated the acetylation of L-ascorbic acid. In the course of this work 5,6-diacetyl-L-ascorbic acid was isolated; however, it is very difficult to obtain in crystalline form. This is obviously the reason why previous investigators failed to isolate acetyl derivatives of L-ascorbic acid. It took months to obtain the compound in crystalline form, but once crystals were isolated, it proved to be easy to prepare large amounts of the compound by a simple procedure.

The treatment of L-ascorbic acid with hot acetic anhydride yielded a non-crystallizable syrup, which did not decolorize iodine. This behavior indicates that the compound may represent a tri- or tetra-acetyl derivative. On prolonged standing, crystals formed in the syrup, which proved to be 5,6-diacetyl-L-ascorbic acid. The structure is represented by formula I which is in agreement with the properties. The diacetyl derivative consumes the calculated amount of iodine, and it titrates as a monobasic acid with alkali. Both reactions are proof that the enediol system must be free.



¹ Present address: William R. Warner and Co., New York, N. Y.

The method by which the compound was obtained for the first time is not of any preparatory importance. A satisfactory method of preparation was later found in the use of sulfuric acid as catalyst. At the time when these experiments were carried out, the use of conc'd sulfuric acid was not an obvious method, because sulfuric acid caramelizes and destroys ordinary sugars easily. Addition of small amounts of conc'd sulfuric acid to a cold suspension of L-ascorbic acid in acetic anhydride causes a spontaneous rise in temperature, and solution of the L-ascorbic acid. On seeding, 5,6-diacetyl-L-ascorbic acid crystallizes slowly.

The yield of 5,6-diacetyl-L-ascorbic acid is about 50%. An excellent solvent for the recrystallization was found in nitromethane, which surprisingly enough, is not reduced by 5,6-diacetyl-L-ascorbic acid at the temperatures necessary for recrystallization. 5,6-Diacetyl-L-ascorbic acid is stable when kept protected from air and moisture. It keeps indefinitely in an evacuated desiccator containing a drying agent. In ordinary stoppered bottles even the carefully dried compound decomposes slowly, and the characteristic odor of acetic acid appears soon. At the same time, the originally colorless material turns yellow and cakes, but such samples may still contain more than 90% of unchanged material.

In water the compound is not very stable. However, small amounts may be recrystallized from hot water, yielding beautiful prisms.

It is noteworthy that the same procedure did not succeed in attempts to prepare an acetyl derivative of D-isoascorbic acid.

EXPERIMENTAL

First isolation of crystallized 5,6-diacetyl-L-ascorbic acid. Seventeen and six-tenths grams of L-ascorbic acid (0.1 mole) was heated in 40.8 g. of acetic anhydride (0.4 mole) on an oil-bath to about 130° for 20 minutes. At about 110° a vigorous reaction occurred and the L-ascorbic acid dissolved completely. Heating was continued for an additional two hours at 110–115°. The solvent was then removed *in vacuo*. A thick, light amber syrup remained, which did not reduce iodine. It was triturated with absolute ethanol and the solvent was removed *in vacuo*. This procedure was repeated twice. The syrup was kept in a desiccator for about a month, when it smelled strongly of acetic acid and a sample reduced iodine. On prolonged standing in an evacuated desiccator for several more weeks, crystals started to form. Scratching induced crystallization throughout the syrup. It was then placed in the refrigerator, and after one day a solid mass of crystals had formed. They proved to be 5,6-diacetyl-L-ascorbic acid.

Preparation of 5,6-diacetyl-L-ascorbic acid. In a five-liter three-necked flask equipped with a condenser, stirrer, and thermometer were introduced 880.6 g. (5 moles) of L-ascorbic acid and 1123 g. (11 moles) of acetic anhydride. One drop of concentrated sulfuric acid was added to the stirred mixture. A vigorous reaction took place, the temperature rising to 125° within approximately 10 minutes after the addition of the sulfuric acid. The L-ascorbic acid dissolved at the same time. The resulting solution contained 5,6-diacetyl-L-ascorbic acid. The compound did not, however, crystallize from this solution, even after standing for months. The failure of previous investigators to obtain an acetyl derivative of L-ascorbic acid was obviously due to these poor crystallization properties.

If the solution was seeded at room temperature with crystals of 5,6-diacetyl-L-ascorbic acid and set aside, crystallization started within a few days. After about three weeks approximately 25% of the theoretical amount of the diacetyl derivative had crystallized and was filtered. From the mother liquor, 5,6-diacetyl-L-ascorbic acid continued to crystallize slowly, yielding approximately another 25% of the theoretical amount in two

months. The crude compound was triturated with ether to remove the thick syrupy mother liquor. The crude diacetyl derivative was dried *in vacuo* over sulfuric acid. This crude material melted at 151–154° (uncorr.) and gave the following analysis:

100 mg. used 7.4 cc. *N*/10 iodine (calc'd 7.68 cc.)

100 mg. used 3.87 cc. *N*/10 sodium hydroxide (calc'd 3.84 cc.)

Recrystallization. Five grams of crude 5,6-diacetyl-L-ascorbic acid was dissolved in 6 cc. of boiling nitromethane. From the filtered solution 4.5 g. (about 90%) crystallized on cooling. The melting point is 156–157° (uncorr.).

Anal. Calc'd for $C_{10}H_{12}O_6$: C, 46.16; H, 4.65; mol. wt. 260.20.

Found: C, 46.45; H, 4.81.

Iodine Titration: 100 mg. used 7.75 cc. *N*/10 iodine

Calc'd 7.68 cc. *N*/10 iodine

Acid Titration: 100 mg. used 3.87 cc. *N*/10 sodium hydroxide

Calc'd 3.84 cc. *N*/10 sodium hydroxide

Recrystallization is also possible from 10 parts of ethyl acetate, giving about 55% recovery in beautiful prisms, and from 0.6 parts of water, yielding large crystals in about 60% yield. Specific Rotation: $[\alpha]_D^{25}$ 64.15° (c, 4.9, water). Acidity: pH = 2.44 (c, 5, water). Solubility at 24°: acetic acid approx. 10%; alcohol approx. 25%; ether approx. 0.4%; ethyl acetate approx. 4.5%; nitromethane approx. 5%; water approx. 25%.

Stability. The stability of the compound was determined by iodine titrations and acid titrations. When stored in an evacuated desiccator over calcium chloride or sulfuric acid, the titrations showed no change after a period of 6 months. Under all other conditions (in stoppered bottles, under nitrogen) the acetyl groups are slowly split off.

SUMMARY

L-Ascorbic acid yields, on treatment with acetic anhydride and small amounts of sulfuric acid, the easily-crystallized 5,6-diacetyl-L-ascorbic acid of m.p. 156–157° (uncorr.).

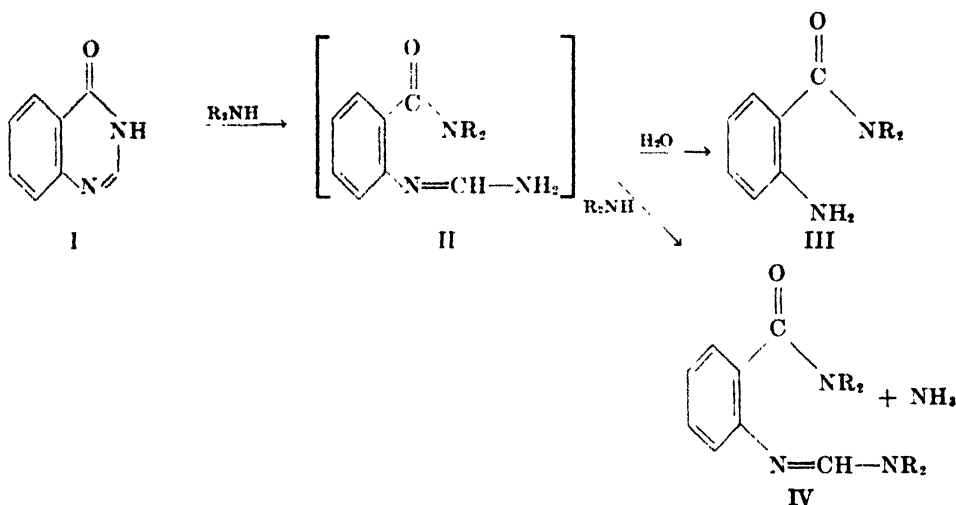
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REACTIONS OF 4-QUINAZOLONE. III. REACTION WITH SECONDARY AMINES¹NELSON J. LEONARD, WILLIAM V. RUYLE, AND LOREN C. BANNISTER²*Received August 18, 1947³*

In order to test the hypothesis (1) that the reaction of 4-quinazoline (I) with amines proceeds by an initial ring-opening, the reaction of 4-quinazoline with secondary aliphatic amines was investigated. The nature of the products obtained indicates that ring-opening between the 3- and 4-position occurs initially and that the 3-N atom of 4-quinazoline is eliminated as ammonia.



In the course of the reaction of a secondary amine with 4-quinazoline, an amidine of type II would be the expected intermediate (1). Compound II could not undergo ring-closure to form a substituted 4-quinazoline but would be expected to yield the N-(2-aminobenzoyl)dialkylamine III on hydrolysis. Such a product was obtained from the reaction of 4-quinazoline with morpholine or piperidine when water was present in the reaction mixture. With morpholine containing water, the compound obtained was N-(2-aminobenzoyl)morpholine (III, $R_2 = -CH_2CH_2OCH_2CH_2-$), identified by mixed melting point with the reduction product of N-(2-nitrobenzoyl)morpholine. With moist piperidine, N-(2-aminobenzoyl)piperidine (III, $R_2 = -CH_2CH_2CH_2CH_2CH_3-$) was formed and was identified in a similar manner.

Under rigorously anhydrous conditions, the reaction of 4-quinazoline with piperidine produced a compound which had an elementary analysis, infrared

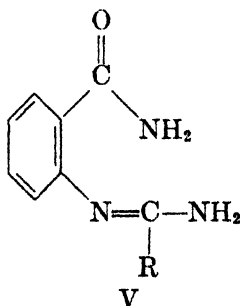
¹ For the first and second articles in this series, see Leonard and Curtin, *J. Org. Chem.*, **11**, 341, 349 (1946).

² Present address: Monsanto Chemical Company, St. Louis, Mo.

³ Revised manuscript with additional experimental results received June 14, 1948.

absorption spectrum, and molecular weight consistent with the structure IV ($R_2 = -CH_2CH_2CH_2CH_2CH_2-$). That compound IV might be formed from II by reaction with excess amine is not unlikely, as it is a well-established fact that certain amidines react with amines in this manner (2). An unequivocal synthesis of IV has not been accomplished although many attempts have been made. Compound IV was insoluble in water but soluble in dilute hydrochloric acid. When the compound was heated under reflux with twenty per cent hydrochloric acid or ten per cent aqueous-alcoholic sodium hydroxide it was unchanged. With sixty per cent sulfuric acid, compound IV was cleaved to piperidine (two moles per mole of IV), identified as the hydrochloride, and anthranilic acid. Treatment of IV with hot acetic anhydride gave N-(2-acetylaminobenzoyl)piperidine.

While the behavior of secondary aliphatic amines has demonstrated the occurrence of initial ring-opening of 4-quinazalone by amines, the identity of the postulated intermediate (II) has not been proved. Careful investigation of the reaction mixtures from many runs of 4-quinazalone with piperidine failed to reveal the presence of any compound II. During the reaction, piperidine evidently caused conversion to IV, or water, to III. In considering an N-arylformamidine as an intermediate in the ring-opening of 4-quinazalone by a primary alkylamine followed by ring-closure (of the N-arylformamidine or of the derived N-aryl-N'-alkylformamidine) to a 3-substituted 4-quinazalone (1), it should have been pointed out that amidines of closely analogous type have previously been described as intermediates in the synthesis of 2-substituted



4-quinazolones. The hydrochloride of the amidine V was suggested by Holljes and Wagner (3) to be the intermediate in the synthesis of 2-alkyl-4-quinazolones from anthranilamide hydrochloride and alkyl cyanides. The same workers proposed an amidine of type V as the intermediate in the reaction of anthranilic acid and acetonitrile in a sealed tube to give 2-methyl-4-quinazalone (4). It is of interest that no reference could be found in the literature to any N-arylformamidine (type II).

EXPERIMENTAL⁴

N-(2-Nitrobenzoyl)piperidine. The method of Franchimont, Van Rijn, and Friedmann (5) was adapted for this preparation. To 8.5 g. (0.1 mole) of piperidine and 5.25 g. (0.13

⁴ All melting points are corrected. Microanalyses by Miss Theta Spoor. Infrared absorption spectra determinations by Mrs. James L. Johnson.

mole) of sodium hydroxide in 40 ml. of water, 2-nitrobenzoyl chloride (from 0.1 mole of 2-nitrobenzoic acid) was added dropwise with stirring during 30 minutes. The yellow oil which formed was separated from the aqueous layer, which was extracted with three 10-ml. portions of benzene. After the combined extracts and oil had been washed with water and dried over potassium carbonate, the benzene was removed, and the residue was recrystallized from benzene-petroleum ether. The yield was 11.5 g. (49% based on 2-nitrobenzoic acid) of crystals, m.p. 51–53° (lit., 56°). This material was reduced without further purification.

N-(2-Nitrobenzoyl)morpholine. This compound, which apparently has not been previously reported, was prepared by the same method as that used for *N*-(2-nitrobenzoyl)piperidine. The yield from 16.8 g. (0.1 mole) of 2-nitrobenzoic acid was 15.5 g. (66%) of colorless prisms, m.p. 122–122.5°.

Anal. Calc'd for $C_{11}H_{13}N_2O_4$: C, 55.93; H, 5.12; N, 11.86.

Found: C, 55.79; H, 5.10; N, 11.82.

N-(2-Aminobenzoyl)piperidine. *N*-(2-Nitrobenzoyl)piperidine (6.25 g., 0.028 mole) was dissolved in 200 ml. of ethanol, 0.2 g. of platinum oxide catalyst was added, and the hydrogenation was carried out at 25° and 3–4 atmospheres. The catalyst and solvent were removed and crystallization of the residue was induced by trituration with petroleum ether. Recrystallization, first from ethanol, then from petroleum ether, gave 4.35 g. (79%) of colorless needles, m.p. 77–78°. The melting point was previously reported as 73–74° (3).

The *acetyl* derivative was prepared by heating under reflux with acetic anhydride. Recrystallization from petroleum ether gave colorless prisms, m.p. 132–132.5°, in 57% yield.

Anal. Calc'd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.38.

Found: C, 68.45; H, 7.39; N, 11.24.

N-(2-Aminobenzoyl)morpholine. This compound was obtained in analogous manner by the hydrogenation of *N*-(2-nitrobenzoyl)morpholine. Recrystallization from methanol, then from petroleum ether, gave colorless needles, m.p. 74–75°, in 53% yield.

The *acetyl* derivative was prepared by heating under reflux with acetic anhydride. Recrystallization from petroleum ether gave colorless elongated prisms, m.p. 133–135°, in 41% yield.

Anal. Calc'd for $C_{14}H_{16}N_2O_3$: C, 62.88; H, 6.50.

Found: C, 62.65; H, 6.42.

Reaction of 4-quinazolone with moist morpholine. A mixture of 7.0 g. (0.048 mole) of 4-quinazolone and 17 g. (0.0195 mole) of morpholine (containing ca. 3% water) was heated under reflux for 44 hours in an oil-bath maintained at 140–150°. Excess morpholine was removed by distillation under reduced pressure. The residual oil was shaken with 50 ml. of 2.5 *N* sodium hydroxide and 50 ml. of benzene and the layers were separated. The aqueous layer was extracted with three 25-ml. portions of benzene. When the aqueous layer was neutralized, no 4-quinazolone separated. The combined benzene extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. The residual oil crystallized slowly. Recrystallization from benzene-hexane yielded 5.11 g. (52%) of colorless needles, m.p. 74–75°.

Anal. Calc'd for $C_{11}H_{14}N_2O_2$: C, 63.75; H, 6.81; N, 13.52.

Found: C, 63.64; H, 6.87; N, 13.60.

The combined mother liquor from several recrystallizations was passed through a column of activated alumina. Successive elutions with 100 ml. of benzene and 100 ml. of ether yielded a further small quantity of the same material. The melting point was not depressed when the compound was mixed with *N*-(2-aminobenzoyl)morpholine, and the melting point of the *acetyl* derivative (133–135°) was not depressed when mixed with *N*-(2-acetylaminobenzoyl)morpholine.

Reaction of 4-quinazolone with moist piperidine. A mixture of 6.5 g. (0.044 mole) of 4-quinazolone and 18 g. (0.212 mole) of piperidine (containing ca. 5% water) was heated under reflux for 42 hours in an oil-bath maintained at 130–140°. Excess piperidine was removed by distillation under reduced pressure. The residual oil was shaken with 40 ml. of benzene and 25 ml. of 2.5 *N* sodium hydroxide. The layers were separated and the

aqueous layer was extracted with three 25-ml. portions of benzene. When the aqueous layer remaining was carefully neutralized with dilute hydrochloric acid, 2.87 g. of 4-quinazolone was obtained. The benzene extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. The residual oil crystallized slowly in a vacuum desiccator over concentrated sulfuric acid. The crude product was triturated with 200 ml. of hexane and then recrystallized repeatedly from hexane to give 1.65 g. (33% based on unrecovered 4-quinazolone) of colorless needles, m.p. 77.5–79°.

Anal. Calc'd for $C_{12}H_{10}N_2O$: C, 70.55; H, 7.90; N, 13.72.

Found: C, 70.69; H, 8.03; N, 13.78.

The hexane mother liquor was passed through a column of activated alumina. Elution with benzene yielded only a further quantity of the same material. The melting point was not depressed when the compound was mixed with *N*-(2-aminobenzoyl)piperidine, and the melting point of the *acetyl* derivative (132–132.5°) was not depressed when mixed with *N*-(2-acetylaminobenzoyl)piperidine.

When anthranilic acid was treated with piperidine and the crude product was worked up under scrupulously identical conditions throughout, no *N*-(2-aminobenzoyl)piperidine could be isolated and most of the anthranilic acid was recovered unchanged.

Reaction of 4-quinazolone with dry piperidine. The piperidine used in this experiment was dried over five changes of crushed potassium hydroxide and redistilled. The 4-quinazolone was dried to constant weight at 80° and kept in a desiccator.

A mixture of 15.0 g. (0.102 mole) of 4-quinazolone and 45 g. of piperidine (0.51 mole) was heated under reflux for forty-eight hours in an oil-bath maintained at 140°. Excess piperidine was removed by distillation under reduced pressure. The residue, which partially solidified on cooling, was digested with 75 ml. of boiling anhydrous ether. The solid was digested with 150 ml. of benzene, and the mixture was cooled and filtered. The residual solid material weighed 5.07 g. and melted at 213–215°. It was shown by mixed melting point to be 4-quinazolone. Evaporation of the benzene solution left a residue that was mostly 4-quinazolone (0.61 g.). Evaporation of the ether solution left 15.52 g. of viscous brown oil, which was triturated with a little high petroleum ether and placed in the refrigerator. Crystallization took place slowly. When the partially crystalline material was dissolved in 25 ml. of hot benzene and cooled briefly, more 4-quinazolone (0.39 g.) separated. The filtrate was concentrated to small volume and the residue was dissolved in hot benzene-petroleum ether mixture. The solvent was decanted from the viscous oil that separated upon preliminary cooling, and upon further cooling, light yellow prisms were deposited. Repetition of this process several times finally yielded 4.32 g. of colorless hexagonal prisms, m.p. 91.5–93°.

Anal. Calc'd for $C_{13}H_{12}N_2O$: C, 72.20; H, 8.42; N, 14.03; mol. wt., 299.

Found: C, 72.03; H, 8.30; N, 14.14; mol. wt. (Rast), 308.

In subsequent experiments it was found that the crystalline product could be isolated more conveniently if the unchanged 4-quinazolone was removed from the reaction mixture by extraction with alkali. Several grams of very viscous material remained after the isolation of the crystalline compound. This material resisted purification by recrystallization or distillation, and also resisted hydrolysis by refluxing with 20% hydrochloric acid.

The pure compound $C_{13}H_{12}N_2O$ was likewise resistant to hydrochloric acid hydrolysis. It was unchanged by refluxing with 20% hydrochloric acid or with 10% aqueous-ethanolic sodium hydroxide for two hours. It was readily soluble in alcohol, ether, and benzene, and insoluble in water and petroleum ether. It dissolved quickly in dilute hydrochloric acid, from which it separated upon neutralization with alkali. The hydrochloride could be formed in anhydrous ether solution, but it was very hygroscopic and appeared to lose hydrogen chloride rapidly.

Hydrolysis of $C_{13}H_{12}N_2O$ (IV) with sulfuric acid. A mixture of 8 ml. of 60% sulfuric acid and 1.01 g. of the compound $C_{13}H_{12}N_2O$ (IV) was heated under reflux for sixteen hours. After cooling, 10 ml. of water was added and the mixture was made distinctly alkaline with 20% sodium hydroxide solution (ca. 21 ml.). The mixture was distilled into 40 ml. of 10%

hydrochloric acid until about 15 ml. of distillate had been collected. Twenty ml. of water was added to the distilling flask, and 20 ml. more of distillate was collected. This process was repeated. The acid solution containing the distillate was evaporated to dryness. The residue, after drying *in vacuo*, weighed 0.99 g. and melted at 160–220°. After two recrystallizations from ether-ethanol, colorless needles were obtained which melted at 236–240°. This melting point was not depressed by admixture of the product with authentic piperidine hydrochloride. The yield was 0.65 g. or 79% of theoretical assuming the liberation of two moles of piperidine by hydrolysis of $C_{18}H_{23}N_3O$. The residue left after evaporation of the mother liquors consisted of impure aniline hydrochloride, which was converted to the base and thence to acetanilide, identified by melting point and mixed melting point, 114–115°.

In another hydrolytic cleavage of the compound $C_{18}H_{23}N_3O$, 0.5 g. was heated under reflux with 2 ml. of 60% sulfuric acid for four hours. Upon cooling, colorless leaflets separated, which were collected and washed with absolute ethanol and ether. When this substance, apparently the sulfate of anthranilic acid, was dissolved in a small quantity of water and the pH of the solution was adjusted to 5.0–5.5, anthranilic acid separated and was identified by melting point and mixed melting point, 143–144°. These hydrolytic products are consistent with the assignment of the structure N-(*o*-1-piperidylformiminobenzoyl)-piperidine to $C_{18}H_{23}N_3O$.

Reaction of $C_{18}H_{23}N_3O$ (IV) with acetic anhydride. One-half gram of the compound $C_{18}H_{23}N_3O$ was heated one-half hour under reflux with 2.5 ml. of acetic anhydride. The excess anhydride was decomposed by the addition of 10 ml. of water to the hot solution. After cooling, the solution was made alkaline and extracted with ether. The residue from the evaporation of the ether solution was recrystallized three times from petroleum ether (b.p. 60–90°). Small colorless prisms were obtained which were identified as N-(2-acetylaminobenzoyl)piperidine by melting point and mixed melting point, 131.5–132.5°.

Infrared absorption spectra In the infrared absorption spectrum of N-(*o*-aminobenzoyl)-piperidine (III, $R_2 = -CH_2CH_2CH_2CH_2CH_2-$), the N—H stretching frequencies appear at 3437 and 3350 cm^{-1} , the amide C=O stretching frequency, at 1613 cm^{-1} ; the characteristic phenyl frequencies, at 1586, 1554, and 1493 cm^{-1} and at 768 cm^{-1} in the long wavelength region of *o*-substituted phenyl. Comparison of the spectrum of N-(*o*-1-piperidylformiminobenzoyl)piperidine (IV, $R_2 = -CH_2CH_2CH_2CH_2CH_2-$) with that of III indicates that the proposed structure is probably correct. No absorption appears in the region of N—H or O—H stretching vibrations. The absorption band in the amide C=O region is strong and broad, between 1628 and 1616 cm^{-1} . Since conjugated C=N stretching frequencies also would appear here, it seems likely that both are present. The characteristic phenyl frequencies are very close to those of III: 1587, 1564, 1492 cm^{-1} and at 757 cm^{-1} in the long wavelength region.

SUMMARY

In an extension of the study of the reaction of 4-quinazolone with amines, the nature of the products obtained with secondary aliphatic amines shows that initial ring-opening must occur.

URBANA, ILL.

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THE MECHANISM OF THE CONDENSATION OF PICOLINE
METHIODIDES WITH AROMATIC ALDEHYDES: A
NEW TYPE OF STERIC HINDRANCE

ARTHUR P. PHILLIPS

Received February 9, 1948

In a recent publication (1) the author presented a correlation between the color, yield, and resonance structure in the products of reaction of aromatic aldehydes with α -picoline methiodide. In discussing the variations of yields with the various aldehydes use was made of an interesting mechanism suggested by Mills (2). His mechanism was used at that time because: (a) Mills had *proved* beyond question that the reaction, under certain conditions, *could* go in the way he indicated; (b) the results could be explained satisfactorily in terms of it; (c) and the author then had no experimental evidence to indicate any lack in that older mechanism.

Now, however, a closer examination of the subject has led the author to the conclusion that the true mechanism of the reaction differs slightly but fundamentally from that postulated by Mills. Although Mills has proved that the steps he indicated would all work, the conditions in various steps, as isolated by him, were not those prevailing throughout the entire reaction under normal conditions. Furthermore, in at least one of his steps, it seems that several intermediate stages may have been ignored which, according to the more recent concepts of condensation reactions, should be considered. Thus we suggest that although the reaction *can* proceed as Mills indicated under his *artificial* conditions, under the *usual* conditions it follows a somewhat different and simpler course.

A brief outline of Mills' mechanism is shown in Fig. 1 [for a more extensive description see reference (1) or (2)].

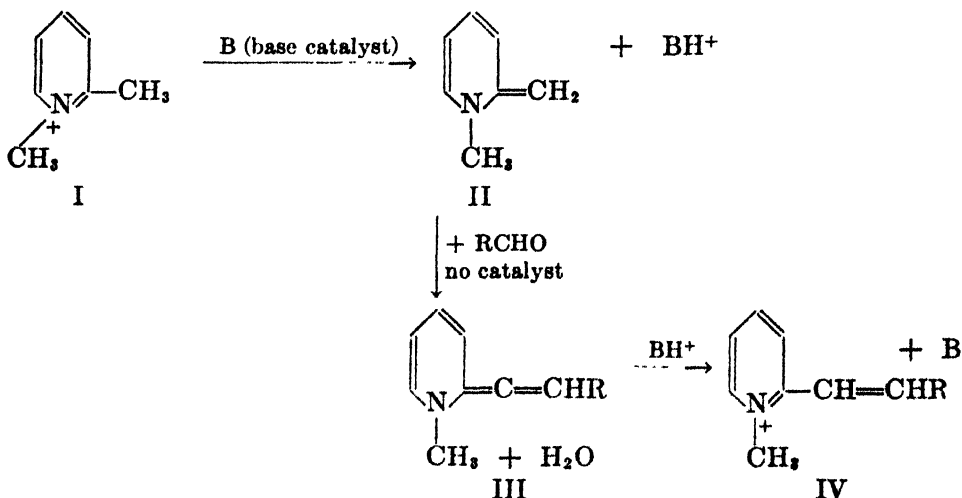


FIG. 1

It is suggested that even under Mills' conditions, where $\text{II} + \text{RCHO}$ react to give III in the absence of a catalyst, it is necessary to insert several intermediate steps. The Fig. 2 sequence is offered as a reasonable one.

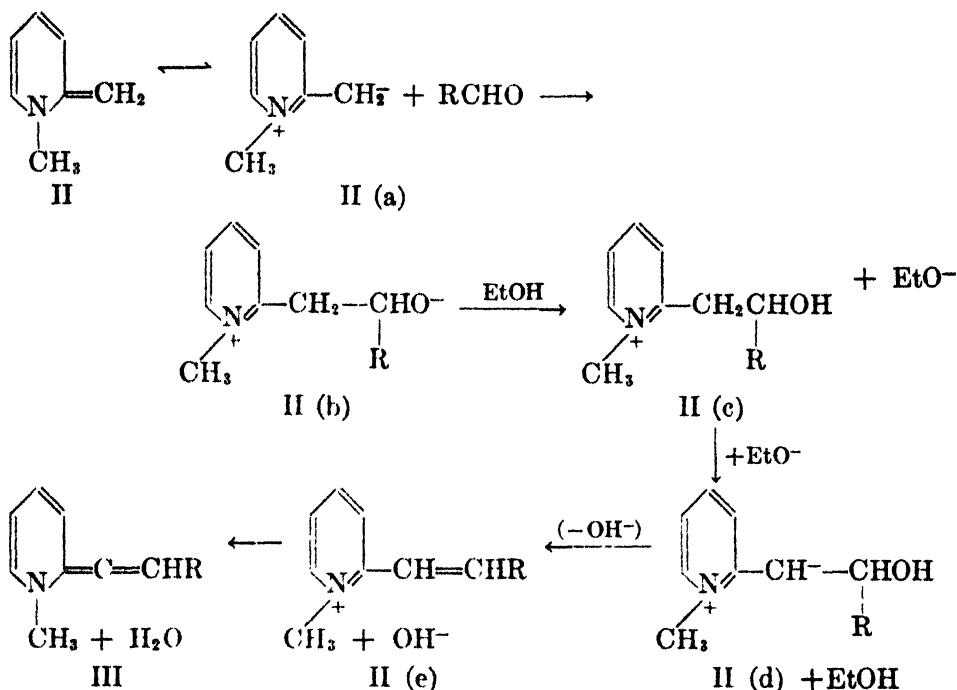


FIG. 2

Although it may not be possible to prove the nature of the mobile intermediates, some such lengthy and laborious process (Fig. 2) probably occurs under Mills' artificial conditions. Here in the absence of a basic catalyst, but in alcohol solution, it has been suggested that perhaps the alcohol may serve as a proton donor and a base catalyst in the transitory steps.

In the normal course of the condensation reaction, however, when piperidine catalyst remains in the reaction mixture, the simpler and more general sequence is suggested as shown in Fig. 3.

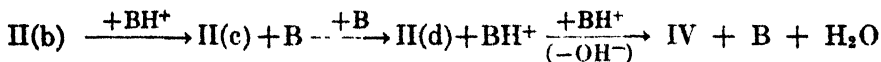


FIG. 3

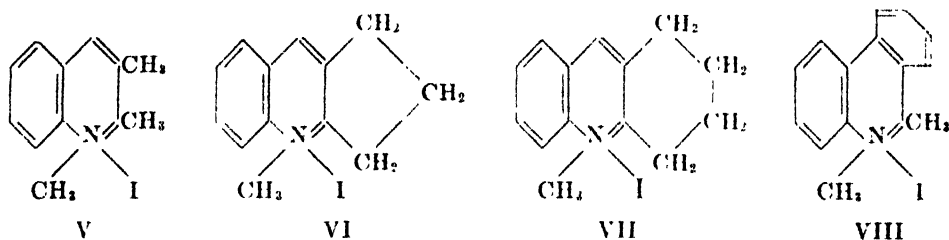
Here II(b) , formed by the nucleophilic attack of the anionic fragment II(a) on the carbon of the aldehyde carbonyl, being a stronger base than piperidine B , abstracts H^+ from the cationic piperidinium ion BH^+ to produce II(c) and B . In the next step piperidine removes a proton from the α -methylene giving II(d) plus BH^+ . The final and decisive step involves the loss of OH^- from II(e) giving the product IV , piperidine, and water.

This process is simply the application of the modern general theory of base catalyzed carbonyl condensations to the particular reaction under consideration.

An innovation has been made, however. Usually in discussions of aldol-like condensations a careful description of the probable mode of formation of the aldol is given, followed by a simple statement that the aldol readily loses water to form the unsaturated product. Although pains are taken to elucidate the mechanism of formation of the aldol, the matter is left hanging there with no follow-up mechanism of the dehydration process, and no indication as to how or why dehydration occurs. In Fig. 3 a reasonable sequence is shown all the way through production of the aldol intermediate and its dehydration to the final unsaturated product.

The experimental basis for the above and for certain further conclusions will now be outlined. If Mills' mechanism were correct it should follow that the methiodides of higher α -alkylpyridines or quinolines should be incapable of condensation under the usual conditions. Thus α -ethylpyridine methiodide and homologous compounds should not react. We have now made α -ethylpyridine methiodide and α -phenethylpyridine methiodide and neither of these, under the usual reaction conditions, gave even a trace of a condensation product with *p*-dimethylaminobenzaldehyde, and both aldehyde and alkylpyridine methiodide components were recovered unchanged from the reaction mixture in essentially quantitative amounts. *p*-Dimethylaminobenzaldehyde, which was used as the aldehyde component as it gave maximum yields with α - and γ -picoline methiodides, was recovered from the reaction mixture as its phenylhydrazone.

These results in themselves would seem to confirm Mills' ideas, but they do not stand alone. Petrow (3) working with somewhat analogous types of compounds in the quinoline and acridine series has reported some observations which seem highly significant in this connection. He has found that under the usual



conditions (alcohol solution, piperidine catalyst), the compounds V, VI, VII, and VIII reacted with *p*-dimethylaminobenzaldehyde as follows: V and VI gave in the vicinity of 70% yields of the stilbazole-like products (analogous to the product obtained from α -picoline methiodide) while VII and VIII gave absolutely no condensation under those conditions, even when the severity of the reaction conditions was increased by the use of higher-boiling alcohols as solvent and longer reflux periods or by fusing the reactants and catalyst at elevated temperatures. [Using a different set of conditions suggested earlier by Shaw and Wagstaff (4) for condensation with the tertiary bases, and applied by him to the quaternary salts, Petrow obtained nearly quantitative yields of the corresponding stilbazole-like products from each of the four compounds, V, VI, VII, and VIII. His modification of the reaction involved heating the reactants for five

to ten minutes in refluxing acetic anhydride.] However, most important for our purpose are his results under the usual condensation conditions. (Results obtained under the other conditions indicate that by the proper application of force the reactions can be made to go.)

Compound VI did react normally to give a considerable yield (though substantially less than the simple α -methyl derivatives gave) of the stilbazole-like product, and there seems to be no reason obvious to this author for considering the mechanism here to be any different from that prevalent with the methyl compounds, since the reaction conditions were similar. The fact that *one* higher homolog has been found which does react normally under the usual conditions, combined with the fact that the mechanism now being presented offers a simpler and more reasonable course of the reaction according to recent views, would seem to indicate that for the normal reaction, Mills' mechanism probably should now be modified in favor of the present one.

Other things remain to be clarified, notably the failure of reaction with compounds VII, VIII and with α -ethyl- and α -phenethyl-pyridine methiodides. In seeking an explanation for the unexpected non-reactivity of these compounds it seemed pertinent to review the principal factors known to influence reactivities of organic molecules: (a) electronic; (b) resonance; and (c) steric factors. It is fully appreciated that here, as in many other types of reactions, probably no one factor is solely responsible for variations in reactivity. If we assume a single mechanism as proposed here, under the normal reaction conditions, and if we then arrange representatives of varying structure of one reactant and compare their reactivities toward a common second reactant it rapidly becomes apparent what is probably the greatest source of variation in this series. Thus with *p*-dimethylaminobenzaldehyde and two to four hours refluxing in alcohol solution with piperidine catalyst the following methiodides gave the corresponding yields of condensation products: α -methylpyridine methiodide, 98%; compound VI, about 70%; compound VII, 0%; α -ethylpyridine methiodide, 0%. Now in going from α -methylpyridine methiodide to α -ethylpyridine methiodide there should be only slight electronic differences, in a direction, it is true, tending to decrease reactivity, for the electron releasing extra methyl would make the hydrogens on the α -methylene less susceptible to dissociation as protons, but differing so little between α -ethylpyridine methiodide, VI, and VII as to be incapable of explaining reaction in the case of VI. Similarly, it is believed that although resonance factors in the pyridine molecule may be varied minutely by the alterations listed in side chain structure, such changes would be too small to be responsible for such tremendous variations in reactivity, and furthermore again would not account for the positive results with compound VI. In this instance we suggest that the third factor, the steric one, is predominant in controlling the reactivity and it is possible to adduce numerous analogies in support of our belief.

In the case under discussion we have compared the reactivity of a reactive methylene compound with a single carbonyl component (*p*-dimethylaminobenzaldehyde) while changing systematically the structural environment about the

methylene. We suggest the variation in environment is principally steric and for the first analogy suggest a comparison between the reactivities of a series of aromatic carbonyl compounds, varied structurally so as to be analogous to the series of reactive methylenes, with a common second reactant. In view of the N-methyl group present in the series of α -alkylpyridine methiodides the carbonyl series would best be represented by 2-methylbenzaldehyde (as analogous to α -methylpyridine methiodide), by 2-methylacetophenone (as analogous to α -ethylpyridine methiodide), by 7-methyl-1-hydrindone (as analogous to VI), and by 8-methyl-1-tetralone (as analogous to VII). The excellent paper by Kadesch (5) presents extremely interesting results which fall into line with our analogy (for the last three carbonyl components) though it must be remembered that Kadesch compared the reactivities of the carbonyl compounds with the relatively small reactants, methylmagnesium iodide and hydroxylamine. Thus his results are only qualitatively in agreement with ours, for in our case the constant reactant, the aldehyde, was of considerable steric size in its own right. For a closer analogy we should consider some reaction of the above listed series of carbonyl components with a common second reactant, such as a reactive methylene, approximating in steric size the aromatic aldehyde of the converse series. In obtaining data from the literature it has been found that results are available which meet our requirements of showing up a wider divergence of reactivities in the carbonyl series, even in the absence of the methyl group, ortho, on the benzene ring, to the carbonyl substituent.

A satisfactory though not ideally constituted common reactant for comparing the reactivities of the series of carbonyl derivatives is cyanoacetic acid. Shemyakin and Trakhtenberg (6) reported their results of condensation of cyanoacetic acid with a series of aliphatic, alicyclic, and aromatic ketones. They mixed the ketone with two to three moles of the acid in the presence of piperidine and heated for two hours at 100–115°. With those ketones which reacted, the yields were between 70–90% and the products were the unsaturated nitriles resulting presumably by decarboxylation of the intermediate unsaturated cyanoacetic acids. Pertinent to our case, α -hydrindone gave condensation with yields in the range stated, while acetophenone gave no condensation. Although benzaldehyde was not included in their study, it is well known that it gives excellent yields of condensation products with the reactive methylene involved, under a variety of similar, mild conditions (7, 8).

Another common reactant, which in its steric size more closely resembles the common reactant aldehyde of the other series, is aniline. As is well known, benzaldehyde reacts rapidly and extensively with aniline under mild conditions (just mixing at room temperature) to produce the azomethine, benzalaniline, in yields of about 85% within fifteen minutes (9). Although the anil of acetophenone can be made, the conditions for its formation are much more strenuous and yields are much lower. Thus when a mixture of acetophenone with nearly two moles of aniline and a catalytic amount of aniline-zinc chloride double salt was heated in an oil-bath at 160–180° for one-half to one hour, yields of the anil in favorable cases were about 55% (10). Under the conditions for rapid forma-

tion of benzalaniline, no acetophenone anil is formed. No information has been discovered in the literature concerning the formation of anils from α -hydrindone or α -tetralone, though it would be reasonable to suppose they could be formed in yields and with degrees of ease intermediate between the anils of benzaldehyde and acetophenone.

Further confirmatory evidence has been obtained in another analogous case by comparing the reactivities of 2,4-dinitrotoluene and 2,4-dinitroethylbenzene toward condensation with *p*-dimethylaminobenzaldehyde in the presence of piperidine catalyst. With these derivatives, activation of the side-chain methylene appears to be closely similar in kind and degree to that present in the alkylpyridine methiodides. Results reported in the literature indicate that the same correlation between yields, color, and the resonance possibilities of the products may exist in this type of compound as in α -picoline methiodide. Thus Dippy, Hogarth, Watson, and Williams (11) heated equimolar amounts of *p*-dimethylaminobenzaldehyde and 2,4-dinitrotoluene with piperidine as catalyst for three to four hours at 100°, and obtained a 98% yield of the intensely colored stilbene (almost black). Using benzaldehyde under slightly different conditions, employing piperidine catalyst and longer reaction time, Bishop and Brady (12) obtained only 60% of the bright yellow stilbene. We have found that 2,4-dinitroethylbenzene does not condense with *p*-dimethylaminobenzaldehyde under conditions giving nearly quantitative yields with the methyl homolog. We were able to recover nearly completely the unreacted starting compounds, the aldehyde as its phenylhydrazone.

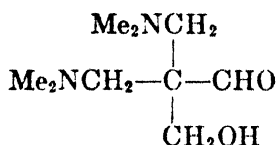
In the dinitroalkylbenzenes *no* classical valence bond intermediates, of the type written and isolated by Mills in the heterocyclic methyl methiodides, can be written. Since such discrete classical valence bond intermediates cannot be written for these compounds we cannot here explain the reactivity or lack of reactivity in terms of the attainability or incapability of attaining structures analogous to II or III. That these two analogous types of reaction are so closely alike in kind, degree, reaction conditions, catalyst, and effect of alkyl group size on reactivity, suggests the two react by the same mechanism. This would strongly support our mechanism and our steric explanation of the lack of reaction in the case of the higher alkyl derivatives.

In accumulating substantiating evidence for the predominantly steric nature of the non-reactivity of the alkyl (higher than methyl) pyridine methiodides and dinitrobenzenes with aromatic aldehydes, another line of approach is obvious. Since in going from a methyl side chain (100% yield) to the ethyl side chain (0% yield) we have already reached the limits of variation of the reactive methylene component, it is conceivable that by decreasing the steric size of the carbonyl component we might obtain condensation in cases where aromatic aldehydes give none. Formaldehyde is probably the most reactive carbonyl compound in general and is unquestionably the smallest.

Making the reasonable assumption that the *mechanism* of carbonyl reaction would not be altered in going over from aromatic aldehydes to formaldehyde it would be expected that in this shift the principal differences in the direction of

Small though the steric requirements of formaldehyde are, after the introduction of two aldehyde groups the composite result of the various effects, electronic and probably mainly steric, is to prevent the introduction of a third aldehyde residue. By the above scheme, reaction with a third molecule of formaldehyde could proceed only to the hydroxymethyl stage anyway.

The illustration used above is an example of the Mannich reaction, for which the mechanism is not known with certainty. Bodendorf and Koralewski (14) have obtained evidence indicating that with dimethylamine and formaldehyde and various reactive methylenes, dimethylaminomethanol is not an intermediate step, and they have also shown that with antipyrine the hydroxymethylantipyrine does not constitute an intermediate, although the methylols of acetone and cyclohexanone do react. We now suggest that in the Mannich reaction it may be impossible to put forward a single mechanism to explain all cases. In line with our present discussion we believe that wherever possible the Mannich reaction mechanism will conform to the above scheme, mediated by a hydroxymethyl reactive methylene compound, which under the reaction conditions, and in the presence of a hydrogen on the carbon β to the hydroxyl and α to the activating group, will dehydrate to the vinyl derivative which then adds the amine to form the Mannich base product. It is well known that a vinyl group α to an unsaturated activating group (CN, COOR, etc.) reacts rapidly and nearly quantitatively with amines. In support of this belief is the work of Mannich and co-workers (15) who with acetaldehyde, for example, have shown that the only product isolated is the following:



Formation of this product agrees with our postulation that the third hydrogen on an activated methyl may react with formaldehyde to form the methylol, but should be incapable of going on to the aminomethyl stage. The fact that such compounds as antipyrine and phenols give good yields of Mannich bases suggest that for these types of reactive "methylenes" an entirely different mechanism must exist.

Our proposed mechanism (for reaction between aromatic aldehydes and picoline methiodides) as contrasted with Mills' mechanism, involves no difference in the type of reaction but only in the degree of reactivity between the α -picoline methiodides and the tertiary bases. On this basis certain analogies with tertiary base reactions should be acceptable as substantiating evidence, both for our mechanism and for the steric nature of lack of reactivity of the higher alkyl derivatives.

On the first of these points the work of Kaplan and Lindwall (16) and other earlier workers (17, 18) has shown that 2-methyl-pyridines and -quinolines react with aromatic aldehydes, either in the presence or absence of a basic catalyst such as piperidine to give aldol-like intermediates, which are stable enough to

be isolated, but which can be dehydrated readily when treated with various dehydrating reagents. We consider this further evidence for our mechanism, for here the aldol intermediates (analogous to IIc) are stable enough for isolation, as might be expected, whereas the greater activation of the α -methylenic hydrogen in the methiodides and the greater resonance stabilization in the dehydration products with the methiodides makes the aldol an unstable intermediate with the latter.

With regard to the second of these points, the steric one, although α -picoline is much less reactive for condensation than its methiodide, on heating at 130–140° for several hours with formaldehyde (the picoline itself probably serving as catalyst here) moderate yields of mono- and di-hydroxymethyl- α -picolines can be obtained, yields of the two depending somewhat on the proportion of formaldehyde used, the temperature, and duration of heating. Little if any trihydroxymethyl compound is produced, though moderate yields of the latter can be obtained by long heating of excess formaldehyde with the mono- or di-hydroxymethyl compounds (19, 20, 21, 22).

With α -ethylpyridine, and depending on temperature and length of heating, formaldehyde yields mainly either the mono- or di-hydroxymethyl compound (22, 23).

These facts indicate that with a smaller carbonyl component reaction with the higher alkylpyridine homologs is no longer excluded.

Under similar reaction conditions γ -methylpyridine appears to be more reactive and gives as the principal product with formaldehyde the trihydroxymethyl compound even when only one mole of formaldehyde is used. With 3-ethyl-4-methylpyridine only the dihydroxymethyl derivative is obtained, probably a consequence of the steric hindrance of the adjacent alkyl (24, 25).

In the reaction of α -picoline methiodide with formaldehyde no discrete products have been isolated, as apparently polymeric resinous products were formed. Using formaldehyde with piperidine under a variety of conditions it has been impossible to isolate a pure crystalline substance, although there was abundant evidence of rapid reaction.

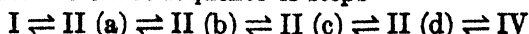
Difficulties involved here are indicated by the fact that 2- β -hydroxyethylpyridine reacts violently with methyl iodide to give mixtures of the methiodides of 2- β -hydroxyethylpyridine and 2-vinylpyridine, neither of which was characterized as such, but only through conversion first to chlorides, which were then isolated as platinichlorides (19).

Further work is in progress exploring the role of steric, resonance, and electronic effects in the reactivities of active methylenes of the pyridine series. An attempt will be made to show whether the difference in reactivity of α - and γ -picolines, as shown by the results with formaldehyde, is associated principally with resonance or steric factors.

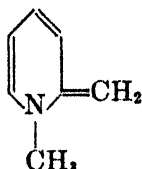
Although we have here postulated a new mechanism for the condensation of aromatic aldehydes with α -picoline methiodide, and with compounds of similar type, this does not in any way negate the correlations between structure and yields stated earlier (1). The facts basic to that correlation remain, and can be

explained equally well in terms of the new hypothesis. All that is necessary is to reword the explanation to fit the new mechanism.

We shall consider the entire sequence of steps



comprising our mechanism as reversible. That the over-all reaction is reversible has been shown by the work of Koenigs, Köhler, and Blindow (26) who, on treating α -stilbazole methiodide with concentrated aqueous alkali, found that benzaldehyde was liberated (isolated and identified as its phenylhydrazone) along with α -pyridonemethide, (which was isolated and identified as its reaction product with carbon disulfide or phenylisothiocyanate).



We still consider that the driving force of the reaction will depend on the increase in resonance stabilization gained in IV over the various starting compounds or intermediates. Thus, considering that the initial steps do occur, formation of II (a) and II (b), as they obviously do with a wide variety of aromatic aldehydes (and there is undoubtedly considerable variation in the ease of reaction at this stage depending on the resonance and electronic structures of the various aldehydes), then regardless of the relative ease of formation of the first mobile intermediate and its successors, the determining factor as to the extent and rate of reaction will lie in the decisive final step in which important resonance within the complete molecule is first possible. The magnitude of the increase in resonance in the final product as compared with that in its precursors determines the extent of the reaction and stability of the product. In the earlier discussion this was expressed in terms of the relative base strengths of the allene intermediate, for attracting protons from BH^+ . According to our new mechanism we would express it in terms of the ease of release of OH^- from the anionic intermediate II (d). This is simply a different form of base strength expressed for a different final intermediate.

The importance of the resonance as a determining factor in the final stage is emphasized by the fact that the yields were best with those aldehydes in which resonance would be most favorable in the products. But in the earlier stages of the reaction sequence, the original nucleophilic attack on the aldehyde carbonyl carbon, the aldehydes giving poorer yields (those substituted with electronegative substituents) would be expected to react most rapidly and completely.

EXPERIMENTAL

α -Ethylpyridine methiodide. α -Ethylpyridine was prepared by the catalytic hydrogenation of α -vinylpyridine using Adams' catalyst in methanolic hydrogen chloride. After two distillations 11 g. of the base, b.p. 146–150°, was treated with 11 cc. of methyl iodide and the mixture was refluxed for four hours. Precipitation of the product with ether gave 25 g.

(100%) of the methiodide, which after recrystallization from ethanol-ether had the m.p. 95–96°.

Anal. Calc'd for $C_8H_{11}IN$: I, 50.98. Found: I, 51.06.

The white crystalline material on standing, even in a closed, dark bottle, rapidly darkened in color and then could not be repurified to obtain any considerable amount of pure colorless substance. Even the pure material could be recrystallized only with some difficulty and usually with considerable losses, especially if manipulations were extended.

α -Phenethylpyridine methiodide. α -Phenethylpyridine was similarly prepared by the hydrogenation of α -stilbazole using Adams' catalyst in methanolic hydrogen chloride. These reductions were performed at 1–3 atm. overpressure of hydrogen at room temperature. The base stilbazoles do not reduce under these conditions in alcohol solution. In the presence of more than a molar equivalent of hydrogen chloride reduction proceeds slowly and is restricted to the side chain double bond or can be stopped at that stage. This is in contrast to the α -stilbazole methiodides which are reduced rapidly in alcohol solution, under the same conditions, to the corresponding phenethylpiperidines. α -Phenethylpyridine, 9 g., plus 6 cc. of methyl iodide in 20 cc. of methanol was refluxed for four hours. On cooling, a pale yellow crystalline product was obtained; yield 12.5 g., (80%). After recrystallization from ethanol the product melted at 190–191°.

Anal. Calc'd for $C_{14}H_{18}IN$: C, 51.68; H, 4.95; I, 39.06.

Found: C, 51.94; H, 4.95; I, 39.19.

*Attempted condensation of α -ethylpyridine methiodide with *p*-dimethylaminobenzaldehyde.*

A mixture of 2.5 g. (0.01 *M*) of α -ethylpyridine methiodide, 2 g. (0.013 *M*) of *p*-dimethylaminobenzaldehyde, and 5 drops of piperidine in 15 cc. of methanol was refluxed for four hours on the steam-bath. The reaction mixture was then evaporated to dryness and unreacted aldehyde was extracted with ether. The ether-insoluble residue, after crystallization from ethanol-ether, gave 2.4 g. (96% recovery) of unreacted α -ethylpyridine methiodide, white crystals, m.p. 89–90°. The ether extract, after evaporation to dryness, was treated with 2 g. of phenylhydrazine in 20 cc. of ethanol and was then heated for thirty minutes on the steam-bath. Cooling this reaction mixture gave 2.9 g. (91% recovery) of the phenylhydrazone of *p*-dimethylaminobenzaldehyde as tan crystals, m.p. 148–149°.

*Attempted condensation of α -phenethylpyridine methiodide with *p*-dimethylaminobenzaldehyde.* (a) A mixture of 1.6 g. (0.005 *M*) of α -phenethylpyridine methiodide, 1.5 g. (0.01 *M*) of *p*-dimethylaminobenzaldehyde and 3 drops of piperidine in 20 cc. of ethanol was refluxed for five hours. After evaporation to dryness the residue was extracted with ether to remove all unreacted aldehyde. The ether-insoluble fraction was crystallized from ethanol and gave 1.6 g. (100%) of recovered, unreacted methiodide, as light orange crystals, m.p. 189–191°.

Anal. Calc'd for $C_{14}H_{18}IN$: C, 51.68; H, 4.95.

Found: C, 51.96; H, 4.66.

The ether extract, after evaporation to dryness, was treated with 2 g. of phenylhydrazine in 20 cc. of ethanol. After heating in the usual way there was obtained 95% of the phenylhydrazone of *p*-dimethylaminobenzaldehyde, m.p. 148–149°.

(b) [Petrov's special conditions (3)]. A mixture of 1.6 g. of α -phenethylpyridine methiodide and 1.5 g. of *p*-dimethylaminobenzaldehyde was added to 50 cc. of boiling acetic anhydride. After refluxing for ten minutes, the chilled reaction mixture gave 1.2 g. (75%) of recovered, unreacted methiodide as yellow crystals, m.p. 190–191°. From the mother liquors only starting materials were obtained.

Attempted condensation of α -phenethylpyridine methiodide with benzaldehyde. A mixture of 1.6 g. (0.005 *M*) of α -phenethylpyridine methiodide, 1.5 g. (0.015 *M*) of benzaldehyde, and 6 drops of piperidine in 20 cc. of ethanol was refluxed two hours. Cooling the reaction mix-

ture gave 1.6 g. (100%) of unchanged starting methiodide as pale yellow crystals, m.p. 189–191°.

Condensation of 2,4-dinitrotoluene with p-dimethylaminobenzaldehyde. A mixture of 3.6 g. (0.02 *M*) of 2,4-dinitrotoluene, 3.0 g. (0.02 *M*) of *p*-dimethylaminobenzaldehyde, and 5 drops of piperidine was heated for four hours on the steam-bath. A solid cake was formed during the reaction. After cooling, this was filtered off, washed with hexane, and gave 6.3 g. (100%) of the stilbene product, m.p. 180–181°.

Attempted condensation of 2,4-dinitroethylbenzene with p-dimethylaminobenzaldehyde. A mixture of 2 g. (0.01 *M*) of 2,4-dinitroethylbenzene (27), 1.5 g. (0.01 *M*) of *p*-dimethylaminobenzaldehyde, and 5 drops of piperidine was heated for five hours on the steam-bath. The reaction mixture was taken up in ether and thoroughly extracted with 4 *N* hydrochloric acid to remove all basic material. Evaporation of the dried ether layer gave 2 g. (100%) of recovered dinitroethylbenzene, as a dark liquid. The aqueous acid solution was basified strongly with 40% potassium hydroxide and extracted with ether. The ether extract was evaporated and the residue on treatment with phenylhydrazine in ethanol gave 92% of the calculated amount of *p*-dimethylaminobenzaldehyde phenylhydrazone, m.p. 148–149°.

SUMMARY

2-Ethyl and 2-phenethyl-pyridine methiodides have been prepared and do not condense with *p*-dimethylaminobenzaldehyde in alcohol solution in the presence of piperidine catalyst. 2,4-Dinitroethylbenzene, likewise, does not condense with the same aldehyde under similar conditions. The methyl homologs under identical conditions gave quantitative yields of condensation products. These data and considerable information available in the literature have been analyzed and interpreted to present a new mechanism for the reaction of aromatic aldehydes with compounds of the type of α -picoline methiodide. The failure of reaction with the higher alkyl homologs has been interpreted as due principally to steric factors, and considerable substantiating information has been brought forth on this point.

TUCKAHOE 7, NEW YORK

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PREPARATION OF THIOPHENE-2-ALDEHYDE AND SOME SUBSTITUTED THIOPHENE ALDEHYDES¹

WILLIAM J. KING AND F. F. NORD

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In the course of studies on the catalytic condensation of carbonyl compounds conducted in this laboratory (1), it was found necessary to prepare thiophene-2-aldehyde as well as certain substituted thiophene aldehydes. The methods for preparing these compounds as recorded in the literature are tedious and result in either low or, at best, fair yields. In Table I are summarized the data on the most important procedures applied in the literature.

The utilization of *N*-methylformanilide in the presence of phosphorus oxychloride for the production of aldehydes has been found applicable with certain carbocyclic and heterocyclic compounds containing particularly reactive positions (12). Since the nuclear sulfur atom in thiophene activates the α -hydrogen atoms, it was thought that this method might be useful in the thiophene series. It was found that thiophene-2-aldehyde could be obtained in 65–70% yields by this procedure, and various substituted thiophene aldehydes in yields ranging from 45 to 85%.

The aldehydes, upon analyses of freshly distilled samples, gave slightly too high values for carbon (range 0.4–0.7%). Therefore, the semicarbazones and acids of these compounds were prepared, and gave entirely satisfactory analyses. The positions of the constituents on the thiophene ring were determined by converting the aldehydes to the corresponding known thiophene carboxylic acids by alkaline permanganate oxidation. The collected data on the compounds prepared are recorded in Table II.

In the application of the *N*-methylformanilide synthesis to 2-bromothiophene, 5-chlorothiophene-2-aldehyde, instead of the expected 5-bromothiophene-2-aldehyde, was obtained, due to the replacement of the bromine atom by chlorine.

The presence of alkyl substituents on the thiophene ring gave rise to higher yields of the aldehyde than was the case with thiophene itself. This is to be expected, as the alkyl groups enhance the activity of the free α -position in the ring and tend to prevent side reactions. On the other hand, the presence of halogen on the ring made the replacement more difficult, and the reaction mixture had to be heated for a longer period of time; furthermore, the over-all yields were somewhat lower. The entering aldehyde group occupied the α -position adjacent to the nuclear sulfur, and in no case was the β -aldehyde isomer obtained.

¹ This investigation was aided, in part, by a grant from the Office of Naval Research. The authors are also indebted to Dr. K. Kavanagh of the Texas Company, New York, for his cooperation.

The analyses were carried out by M. Bier of this Department.

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Attempts to utilize the N-methylformanilide synthesis with 2-nitrothiophene, 2-acetylthiophene, and thianaphthene (benzothiophene) were of no avail. However, it was found possible to prepare thianaphthene-3-aldehyde by the following procedure. Chloromethylation of thianaphthene, although previously reported unsuccessful (15), was effected by employing the method of Darzens

TABLE I
PREPARATION OF THIOPHENE ALDEHYDES AS RECORDED IN LITERATURE

AUTHORS	METHOD	COMPOUND PREPARED	YIELD
Biedermann (2) Barger and Easson (3) du Vigneaud <i>et al.</i> (4)	Acetylation of thiophene to yield 2-acetylthiophene. Then alkaline permanganate oxidation of 2-acetylthiophene followed by decarboxylation of the resulting 2-thiopheneglyoxylic acid.	Thiophene-2-aldehyde	40-50% based on thiophene
du Vigneaud <i>et al.</i> (4) Grishkevich-Trochimovskii (5) Vlastelitz (6) Weygand (7) Gattermann (8)	Iodination of thiophene followed by the action of magnesium and ethyl orthoformate on 2-iodothiophene to yield thiophenealdehyde acetal. Acid hydrolysis yields the free aldehyde.	Thiophene-2-aldehyde 5-Methyl thiophene-2-aldehyde 5-Bromothiophene-2-aldehyde	30-40% based on thiophene 10% based on dibromothiophene
Reichstein (9)	Thiophene, HCN, HCl, anhydrous aluminum chloride at low temperature.	Thiophene-2-aldehyde	10% based on thiophene
Barger and Easson (3)	Rosenmund reduction of 2-thenoyl chloride.	Thiophene-2-aldehyde	10-20% based on thenoyl chloride
Dunn, Waugh, and Dittmer (10) Blicke and Leonard (11)	Thiophene, HCl, and formaldehyde with cooling to yield 2-thienyl chloride. Formation of addition compound with urotropine and subsequent hydrolysis to yield thiophene-2-aldehyde.	Thiophene-2-aldehyde	20-25% based on thiophene

and Lévy (16) with modifications. Then, by formation and subsequent hydrolysis of the urotropine addition product of 3-chloromethylthianaphthene, thianaphthene-3-aldehyde was obtained. Because attempts to chloromethylate 2-nitrothiophene and 2-acetylthiophene proved unsuccessful, this procedure could not be used to obtain the aldehydes from these compounds.

The *one step* synthesis of thiophene aldehydes with good yields should greatly simplify the preparation of certain compounds, in which a benzene ring is re-

TABLE II
THIOPHENE ALDEHYDES PREPARED BY N-METHYLFORMANILIDE SYNTHESIS

STARTING MATERIAL	ALDEHYD ^a				SEMICARBAZONE				ACID			
	Product	Yield, %	B.P., °C./mm.	Anal.				M.P., °C	M.P. in Lit., °C	Calc'd		
				C%	H%	C%	H%			C%	H%	Found
Thiophene	Thiophene-2-aldehyde	65-70	66-67/4	53.55	3.59	53.95	3.75	220-221 ^a	129-130	46.86	3.14	46.75
2-Methylthiophene	5-Methylthiophene-2-aldehyde	80-85	81-82.6	57.11	4.80	57.64	4.71	207-208	137-138	50.69	4.26	50.93
3-Methylthiophene	3-Methylthiophene-2-aldehyde	80-85	83-85.5	57.11	4.80	57.50	4.50	208-209	147-148	50.69	4.26	50.86
2-Ethylthiophene	5-Ethylthiophene-2-aldehyde	75-80	91-92/5	59.97	5.75	60.70	5.17	194-195	71 ^c	53.85	5.15	53.77
2-Propylthiophene	5-Propylthiophene-2-aldehyde	80-85	108-109/5	62.30	6.54	63.03	6.33	186-187	58	56.44	5.92	56.31
2-Chlorothiophene	5-Chlorothiophene-2-aldehyde	50-55	89-90	65.40	96.2	66.41	50.2	37	153-153.5 ^b	36.93	1.86	37.18

^a Ref. (9) gives m.p. 227-228°; Ref. (5) gives m.p. 218-219° (uncor.).

^b Ref. (13).

^c Ref. (14).

placed by a thiophene or substituted thiophene ring. For example, β -2-thienyl-alanine, the isostere of phenylalanine has been prepared from thiophene-2-aldehyde, and used in biological and metabolic studies (3, 4).

EXPERIMENTAL

Materials. Thiophene, 3-methylthiophene, and 2-acetylthiophene were obtained through the courtesy of Dr. W. M. Holaday and Dr. G. A. Harrington of the Socony Vacuum Oil Company; thianaphthene, 2-chlorothiophene, 2-methylthiophene, and 2-nitrothiophene through the courtesy of Dr. L. C. Kemp, Jr. and his associates of the Texas Company; 2-chloro- and 2-bromo-thiophene through the courtesy of the Michigan Chemical Corporation; and 2-nitrothiophene through the courtesy of Dr. N. B. Sommer of the Jefferson Chemical Company. 2-Ethyl- and 2-propyl-thiophene were prepared by a modified Wolff-Kishner reduction of the semicarbazones of 2-acetyl- and 2-propanoyl-thiophene (18). 2-Propanoylthiophene was prepared according to Hartough and Kosak (19).

General procedure for the preparation of thiophene aldehydes. The procedure utilized was essentially the same for all of the thiophene compounds with the exception of 2-chloro- and 2-bromo-thiophene.

Thiophene-2-aldehyde. Thiophene (21 g., 0.25 mole), 48 g. of phosphorus oxychloride (0.31 mole), and 45 g. of N-methylformanilide (0.32 mole) were mixed in a 500-cc. round-bottom flask fitted with a ground glass reflux condenser. The reaction is exothermic, and, if the mixture is allowed to stand for some time, the temperature will slowly rise. However, to reduce the time, it was customary to heat the preparation cautiously on a steam-bath until evolution of hydrogen chloride gas commenced. At this point, heating was discontinued and cooling immediately applied to prevent excessive decomposition. With larger quantities of reactants, some care must be exercised, as insufficient cooling at this point will lower the yield considerably. After the initial reaction had subsided, the reaction mixture was heated for twenty minutes on a steam-bath to complete the reaction. At the end of this period, cooling was again applied and the contents of the flask carefully neutralized with excess aqueous sodium acetate. The mixture was then steam distilled, the distillate extracted with ether, the ether extract washed with 6 *N* hydrochloric acid and with 5% sodium bicarbonate solution, dried over anhydrous sodium sulfate, and rectified. There was obtained 19 g. (68%) of thiophene-2-aldehyde (b.p. 66–67°/4 mm.). The semicarbazones and acids were prepared according to methods already described (17). The acids were purified by recrystallization from water, and finally by sublimation *in vacuo*. The semicarbazones were recrystallized from alcohol.

5-Chlorothiophene-2-aldehyde. 2-Chlorothiophene (35.6 g., 0.3 mole), 66 g. of phosphorus oxychloride (0.43 mole), and 58 g. of N-methylformanilide (0.43 mole) were mixed in a 500-cc. round-bottom flask fitted with a ground glass reflux condenser. Heating on a steam-bath caused only slight evolution of HCl. Therefore, heating was continued with a free flame until the reaction began. The reaction was allowed to proceed without cooling, and after the initial vigorous reaction had subsided, the mixture was heated on a steam-bath for one hour. Following the same isolation procedure described above, there was obtained 22.5 g. (51%) of 5-chlorothiophene-2-aldehyde, (b.p. 89–90°/6.5 mm.). A small prerun of 2-chlorothiophene (3 g.) was recovered during rectification.

When 2-bromothiophene was used as a starting product, 5-chlorothiophene-2-aldehyde was obtained. In this case, 32.58 g. of 2-bromothiophene (0.2 mole), 52 g. of phosphorus oxychloride (0.33 mole), and 45 g. of N-methylformanilide (0.33 mole) were brought into reaction. Heating on a steam-bath caused a vigorous evolution of HCl, and cooling was applied. After the reaction had subsided, the flask was heated on a steam-bath for 1 hour. Following the usual isolation procedure, there was obtained 17 g. of 5-chlorothiophene-2-aldehyde (58%), (b.p. 88–91°/6 mm.). The semicarbazone and acid prepared from this compound showed no depression of melting point when mixed with authentic samples obtained from 5-chlorothiophene-2-aldehyde.

3-Chloromethylthianaphthene. Dry HCl was passed into a suspension of 43 g. of trioxymethylene in 512 g. of acetic acid, until 58 g. was absorbed. Then 134 g. (1 mole) of thianaphthene was added to the clear solution. The solution became warm, and was placed in the icebox overnight. The mixture was then poured into 2 l. of water and extracted with ether. After washing the ether extract with water and 5% sodium bicarbonate solution, drying over sodium sulfate, and rectifying, there was obtained 120 g. of 3-chloromethylthianaphthene, (b.p. 149–156°/11 mm.). Refractionation yielded 116 g. (63%), (b.p. 152–153°/11 mm.) (m.p. 39–40°).

Anal. Calc'd for $C_{12}H_7ClS$: Cl, 19.41. Found: Cl, 19.24.

Thianaphthene-3-aldehyde. 3-Chloromethylthianaphthene (18.25 g., 0.1 mole), 14.02 g. of urotropine (0.1 mole), and 100 cc. of chloroform were refluxed for 1 hour. At the end of this time, the crystalline addition product was filtered off, air dried, and decomposed with 300 cc. of water. The solution was steam distilled and the thianaphthene-3-aldehyde came over slowly. The distillate was extracted with ether, the ether extract washed with water, 5% sodium bicarbonate solution and water again, dried over sodium sulfate, and the ether removed. There was obtained 5.1 g. (31%) of thianaphthene-3-aldehyde. Recrystallization from alcohol gave white crystals, (m.p. 58°). Komppa and Weckman (20) reported 58°.

Anal. Calc'd for $C_{12}H_8OS$: C, 66.63; H, 3.73.

Found: C, 66.88; H, 3.68.

SUMMARY

1. The N-methylformanilide synthesis has been shown to be applicable to the preparation of thiophene-2-aldehyde and some substituted thiophene aldehydes.

2. The following aldehydes and their semicarbazones, which are not listed in the literature, were prepared: 3-methylthiophene-2-aldehyde, 5-ethylthiophene-2-aldehyde, 5-propylthiophene-2-aldehyde, and 5-chlorothiophene-2-aldehyde.

3. 3-Chloromethylthianaphthene was prepared by chloromethylation of thianaphthene. Thianaphthene-3-aldehyde was obtained from 3-chloromethylthianaphthene.

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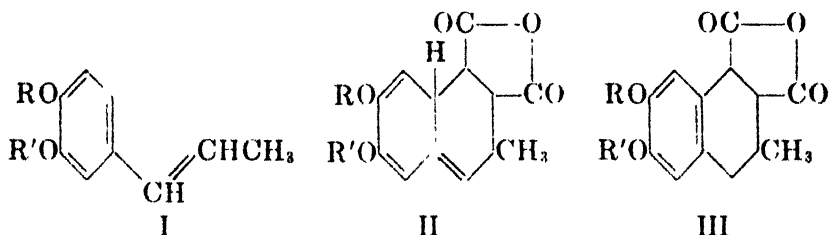
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ADDITION OF MALEIC ANHYDRIDE TO ANETHOLE. I.¹

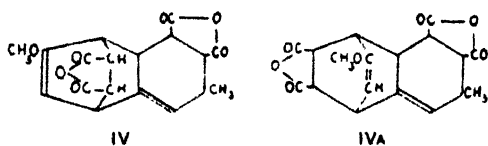
V. BRUCKNER AND J. KOVÁCS

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In a previous communication (1) it was proved in agreement with the statements of Hudson and Robinson (2) that O-methylisoeugenol (Ia) and isosafrole (Ib) produce with maleic anhydride tetrahydronaphthalene derivatives of type III, which must be formed from unstable intermediates of type II. Besides this, one of us (1) found that anethole (Ic) with maleic anhydride gives a crystalline product which contains for 1 mole of anethole 2 moles of maleic anhydride. The formation of this "bis-adduct" was explained in the following manner: the unstable intermediate (IIc) was not stabilized by an aromatic rearrangement but reacted immediately as a conjugated diene; in the sense of the rule of Bredt-Windaus (3), it ought then to give the end product of formula IV.



- a. $R = R' = CH_3$
 b. $R + R' = CH_2$
 c. $R = CH_3$. $R'O = H$

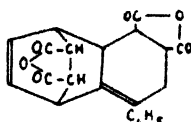


In the reaction of anethole with maleic anhydride, Hudson and Robinson (2) observed only the formation of a heteropolymer product (4). Tamayo and Ayestarán (5) isolated, to judge from all signs, the same product; however, they made the mistake of thinking that they had obtained a regular 1:1-adduct. Nevertheless, the formation of this heteropolymer product dominates this reaction, so that previously (1) it was possible to obtain the bis-adduct in only an 8% yield. Now we have found that different inhibitors can entirely repress the formation of the heteropolymer product in favor of the bis-adduct. If the components are melted with a small amount of dimethylaniline at 80°, a 60% yield of the bis-adduct is obtained.

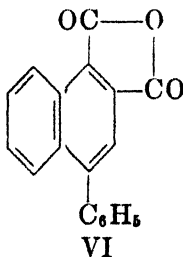
¹ Preliminary report: *Nature*, 1948, in press.

We have reexamined the correctness of formula IV, which was especially indicated by the following two considerations:

A. So far no one has yet exactly proved that it is possible to disturb permanently through a diene synthesis the aromatic character of a mononuclear system. Although Wagner-Jauregg (6) had observed the formation of a bis-adduct in the reaction between 1,1-diphenylethylene and maleic anhydride, and set up first the formula V, later, however, he repudiated (7) the possibility of this formula, without advancing another one. In spite of this, Bergmann *et al.* (8) accepted the correctness of this formula (V), as heating the compound with sulfur gave the naphthalene derivative VI. They also succeeded in converting numerous other 1,1-diarylethylenes in this manner; however, they did not prove conclusively the formulas of the bis-adducts.



B. Hudson and Robinson (2) were of the opinion that naphthalene derivatives are obtained only by a Diels-Alder reaction of styrene derivatives when there is an alkoxy group in the *m*-position to the side chain. The formation of IV through the intermediate IIc is in disagreement with this view.

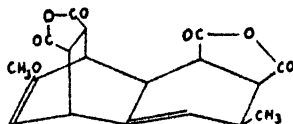


The proof of the correctness of formula IV must first take into account the spatial arrangement. If we assume an *endo-cis* type addition, which has often been proved in Diels-Alder reactions (9), and starting from anethole, which may be supposed to be a *trans*-anethole (10), then we must still take into account the formation of four individual stereomers, *i.e.*, two pairs of antipodes. Formulas VII and VIII show arbitrarily-chosen members of each of the two possible racemates. We obtained a homogeneous bis-adduct, which behaves, as shown below, rather in agreement with formula VIII (and naturally also with its mirror image). Therefore we propose as a simpler manner of design, formula IVa instead of the previously used formula IV.

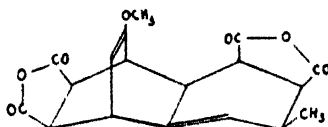
The naphthalene skeleton. On distilling the bis-adduct *in vacuo*, it decomposed into its components: anethole and maleic anhydride. If it was, however, heated in the presence of sulfur, it gave 7-methoxynaphthalene-1,2-dicarboxylic acid anhydride (11). So at higher temperature the diene synthesis becomes reversi-

ble in both its phases, but in the presence of sulfur acting as a dehydrogenating agent, IIc becomes stabilized as a naphthalene derivative without decomposition.

The enol ether character of the methoxyl group. With the calculated amount of 5 *N* sodium hydroxide, the bis-adduct could be quickly saponified even at room temperature; on acidification, an acid was obtained containing a methoxyl group ("A-acid"; m.p. 270–273°), which crystallized as trihydrate and was rather sparingly soluble in hot water. This substance could be converted by treatment with acetic anhydride into the bis-adduct. If the saponification was carried out by boiling with a small excess of alkali, two acids were obtained on acidification; the one which appeared in lesser amount was the A-acid, whereas the other one contained no methoxyl, and was more easily soluble in hot water. The latter ("B-acid"; m.p. 265–270°) crystallized as a tetrahydrate and gave on treatment with acetic anhydride, or by heating, the same anhydride (anhydride of IXb; m.p. 288°), which also could be obtained by treatment of the bis-adduct for a short time with boiling formic acid, and did not contain a methoxyl group. Boiling an aqueous solution of the A-acid leads, in consequence of the easy split-



VII



VIII

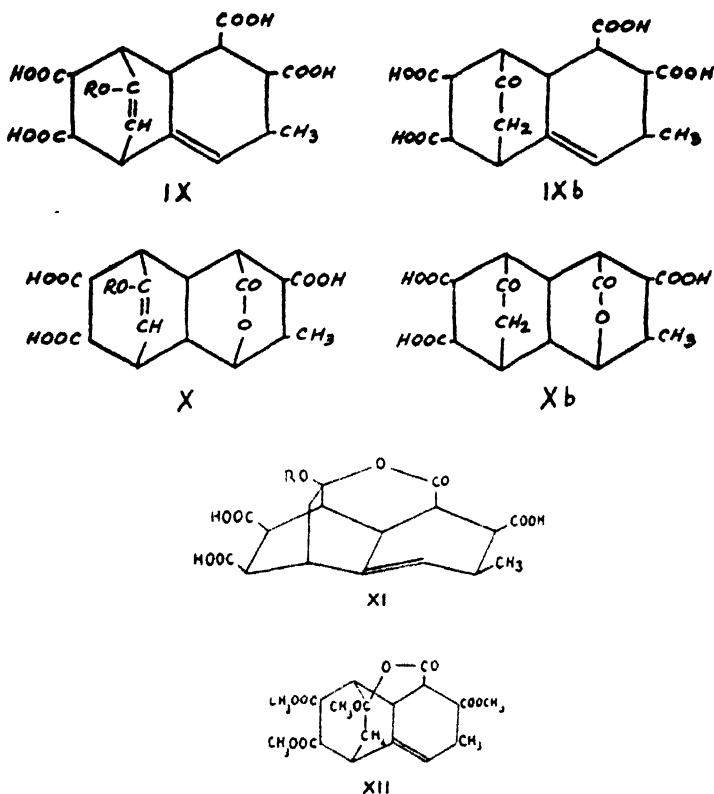
ting of the methoxyl group, to the B-acid. Finally, the easy splitting of this group was also proved by the fact that the bis-adduct could be converted with boiling aniline to the same bis-phenylimide (bis-phenylimide of IXb; m.p. 280–285°) which also could be obtained by a similar treatment of the anhydride, the methoxyl group of which was previously split by boiling with formic acid.

The position of the enol ether methoxyl group. Both acids A and B mentioned above could be sharply titrated with 0.05 *N* sodium hydroxide whereby, however, they showed the presence of only 3 carboxyl groups; the fourth of these groups appeared only during a lactone titration; however, it is possible to split the lactone ring at room temperature. Consequently the acids IXa and IXb (in the latter we can naturally expect a change into the tautomeric keto acid) which are to be derived from formula VIII must contain one of their carboxyl groups in a lactone bond. As the possibility of a lactonization is offered by γ - as well as by δ -unsaturated carboxylic acids (12), also by γ - or δ -oxo acids (13), it is possible to set up different formulas for the lactonized acids. For spatial reasons, some of these formulas are to be preferred, so that as strainless systems there remain only the two types X and XI.

a. R = CH₃

b. R = H

The results of our further investigations seem to support formula XI. Namely, both acids could be esterified with diazomethane, whereby the A-acid (XIa), through consumption of 3 moles of diazomethane formed a lactone methyl ether trimethyl ester (XII; m.p. 178–179°), whereas the B-acid (XIb), through consumption of 4 moles of the reagent, gave a keto acid tetramethyl ester (XIII, m.p. 208–210°). As these esters are isomeric but not identical, we must assume that by the action of diazomethane, the lactone ring of the B-acid (XIb) was opened.



The following experimental facts also support the correctness of this conclusion: (a) ester XIII could also be obtained directly from the bis-adduct (VIII) by boiling it with methanol containing concentrated sulfuric acid; (b) on boiling with formic acid, XII gave by loss of one of its methyl groups a trimethyl ester (m.p. 230–232°) for which we must assume formula XIV, as it shows in alcoholic-aqueous solution, acid reaction, and forms with diazomethane the ester XIII. These reactions, especially the splitting of the lactone ring by diazomethane, agree only with formula XI, and exclude formula X.

In further support of formula XI may be advanced the following evidence: on boiling VIII, XIa, XIb, or XIII for 10–12 hours with 5 *N* hydrochloric acid, an acid (m.p. 260–262°) was formed, which did not contain a methoxyl group. It was isomeric with XIb, and on titration with 0.05 *N* sodium hydroxide showed

sharply 4 carboxyl groups. Obviously we must expect here, just as in the similar treatment of *cis*-hexahydro-*o*-phthalic acid (14), the formation of a *trans* acid, for which we set up formula XV, as it did not form a lactone, and did not

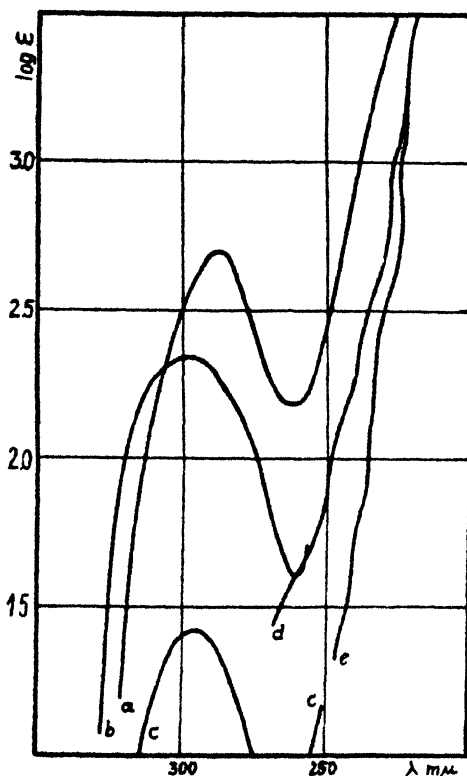
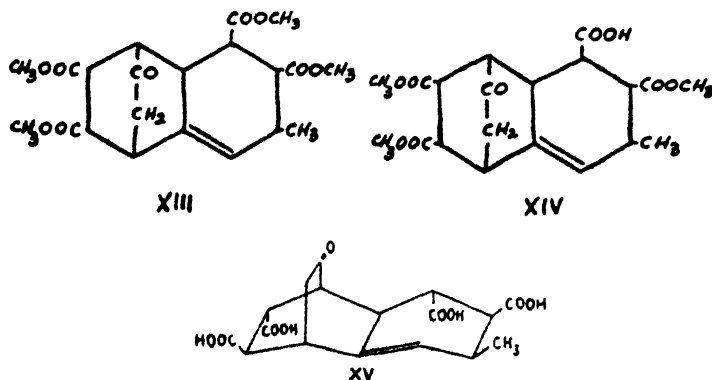


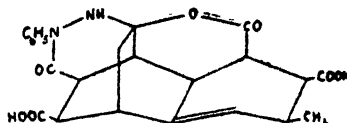
FIG. 1. Ultraviolet spectra of dilute aqueous solutions of XV, curve a; XIa, curve e; XIb, curve d; of dilute chloroform solutions of XV-tetramethyl ester, curve b; XIII, curve c.

give an anhydride when treated with boiling acetic anhydride, but remained unchanged. This *trans* acid produced with diazomethane a tetramethyl ester (m.p. 154°) and gave with hydroxylamine a regular oxime (m.p. 224–225°) containing 4 carboxyl groups. In consequence of their structures, the *trans* acid

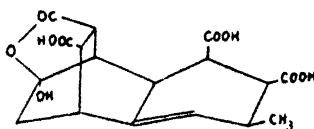
as well as its ester show an ultraviolet absorption spectrum containing the band of the ketone group, which is somewhat displaced towards the long-wave region; the ketone band is also shown by the ester XIII. In accordance with their different structures, the acids XIa and XIb do not show this band (*cf.* Fig. 1).

Decision between the possibilities for the formulas VII and VIII. The experimental facts which have been hitherto stated would also agree with formula VII for the bis-adduct. However, the conversion of the B-acid with phenylhydrazine gave a result which was in better agreement with formula VIII; namely, the B-acid did not form a regular phenylhydrazone but led to a bis-condensed product ($C_{23}H_{26}N_2O_7$; m.p. 180°) which, though it could not be sharply titrated as a dicarboxylic acid, can only contain two carboxyl groups, since it forms with diazomethane a dimethyl ester (m.p. $295-300^\circ$).²

We can therefore state confidently, that in the reaction of the B-acid with phenylhydrazine a double condensation took place, whereby also one of the carboxyl groups disappeared.³ So we come to the conclusion that the product of this condensation must be a dihydropyridazinone derivative (15) of formula



XVI



XVII

XVI. If we accept this formula, we can come to a decision between the two formula possibilities VII and VIII. Namely, the hydroxylactone carboxylic acid (XVII), derived from formula VII, contains a hydroxyl group which can react in *trans* position to each of the 3 carboxyl groups and, therefore, a double condensation can not take place. Because of this we decided in favor of formula VIII, in which only the presence and position of that double link which does not belong to the enol ether group remains to be proved. Investigations concerning this question will be reported later.

EXPERIMENTAL

Action of maleic anhydride on anethole in the presence of dimethylaniline (VIII). A stirred mixture of maleic anhydride (500 g.), anethole (300 g.), and dimethylaniline (8 g.)

² At the moment we are not able to explain the conspicuously high m.p. of this ester in relation to the m.p. of the free acid.

³ The B-acid gives with hydroxylamine hydrochloride in acid medium a condensation product which shows the empirical formula of a regular oxime but behaves as a dibasic acid. By treatment with diazomethane or dimethyl sulfate, this acid forms a compound of much higher nitrogen value than calculated for a regular ester. On melting the condensation product, loss of an additional two moles of water takes place and a dibasic acid is again formed. The structure of all these products must be proved by further investigations.

was heated on a bath at 80° for four hours. From the homogeneous liquid, which became viscous and dark brown, a large amount of crystals separated during the heating. After cooling, the crystalline product was filtered, washed with ethyl acetate until colorless, and dried at 100° *in vacuo*; yield 310 g. (44.5%). It crystallized from ethyl acetate in large colorless prisms containing 0.5 mole of solvent of crystallization, which was lost on heating at 100° *in vacuo* for ten hours; m.p. 241° (dec., beginning at 230°); the same m.p. was observed after many recrystallizations, also with change of solvent.

Anal. Calc'd for $C_{18}H_{16}O_7$: C, 62.8; H, 4.7.

Found: C, 62.7; H, 4.9.

After removal of solvent from the filtrate of the reaction mixture, a dark brown viscous oily residue was obtained (383 g.), which on steam distillation gave 17 g. of anethole. The remaining aqueous solution was concentrated to 500 ml., well cooled, acidified, the crystals washed with 250 ml. of cold water, and dried *in vacuo* at 100°. This procedure led to 132 g. (16.5%) of the B-acid (see below), total yield of the addition, 61%.

A-acid (XIa). Six and nine-tenths grams of the powdered bis-adduct (VIII) was shaken with 16 ml. of 5 *N* sodium hydroxide for five minutes, cooled, acidified with 2 *N* hydrochloric acid, the crystals washed with 80 ml. of ice-cold water, and dried in air; colorless needles, yield 6 g. The substance is sparingly soluble in hot water (1:100), but on cooling, only one-tenth crystallizes, as the main part has been turned into the readily-soluble B-acid (see below). It forms a trihydrate (a), the crystal water of which is completely lost by drying *in vacuo* at 100° (b); m.p. 270–273° (dec.).

Anal. Calc'd for $C_{18}H_{16}O_8 + 3H_2O$: C, 49.8; H, 6.0; CH_3O , 7.1; for $C_{18}H_{16}O_8$: C, 56.8; H, 5.3.

Found: (a) C, 49.8; H, 6.1; CH_3O , 6.9.

(b) C, 56.8; H, 5.4.

Titration⁴ of (a). Calc'd for 3 COOH groups: COOH, 31.1.

Found: COOH, 31.9.

Lactone titration⁵ of (a) Calc'd for 4 COOH groups: COOH, 41.1.

Found: COOH, 39.8.

Conversion of the A-acid into its anhydride (VIII) was carried out by dissolving it in four parts of boiling acetic anhydride and diluting the cooled solution with dry ether. The crystals, after recrystallization from ethyl acetate, show alone and mixed with the bis-adduct (VIII) obtained directly, the m.p. 241° (dec.).

Anal. Calc'd for $C_{18}H_{16}O_7$: C, 62.8; H, 4.7.

Found: C, 63.0; H, 4.8.

B-Acid (XIb). 1. A solution of 6.9 g. of VIII in 20 ml. of 5 *N* sodium hydroxide was boiled for ten minutes, and after acidifying with 10 ml. of 10 *N* hydrochloric acid, cleared with charcoal. On cooling, there separated a mixture of the crystals of both the acids A and B (6 g.), 5 g. of which in 20 ml. of boiling water could be redissolved; the insoluble remainder was the A-acid. The tetrahydrate of the B-acid crystallized from the aqueous solution in colorless large prisms (2.8 g.); they lost their hydrate water by drying *in vacuo* at 100° for three hours; readily soluble in hot water (1:1.8); methoxyl analysis negative; m.p. 265–270° (dec., beginning at 250°).

2. If VIII was boiled with water for a few hours, the B-acid was formed in quantitative yield. For analysis a sample was recrystallized from water and dried (a) in open air until the weight became constant; (b) *in vacuo* at 100° for three hours.

Anal. Calc'd for $C_{17}H_{14}O_8 + 4H_2O$: C, 46.6; H, 6.0; for $C_{17}H_{14}O_8$: C, 55.7; H, 5.0.

Found: (a) C, 46.7; H, 6.2.

(b) C, 55.4; H, 5.2.

Titration of (a). Calc'd for 3 COOH groups: COOH, 30.8.

Found: COOH, 31.1.

⁴ All carboxyl estimations were made by direct titration of hot alcoholic-aqueous solution of 30–50-mg. samples using 0.05 *N* sodium hydroxide and phenolphthalein.

⁵ All lactone titrations were carried out in the customary manner using a solution of 200–350-mg. samples in 10 ml. of *N* sodium hydroxide.

Lactone titration of (a). Calc'd for 4 COOH groups: COOH, 41.1.

Found: COOH, 41.0, 40.9.

Conversion of the B-acid into its anhydride. Bis-anhydride of IXb. 1. A suspension of 2 g. of the B-acid (XIb) in 30 ml. of acetic anhydride was refluxed for a few minutes, and the product after filtering washed with ether. The colorless crystals were recrystallized from nitrobenzene; m.p. 288° (dec. beginning at 275°).

2. On boiling 2 g. of the bis-adduct (VIII) with 20 ml. of formic acid, solution took place at first, but after a few seconds the solution deposited crystals (1.1 g.) which did not contain methoxyl; m.p. alone and mixed with a sample obtained *via* 1., 286° (dec. from 275°).

3. On heating the B-acid (XIb) near its m.p., the same anhydride was obtained as by 1. or 2. Hydrolysis of the substance leads to the B-acid.

Anal. Calc'd for $C_{17}H_{14}O_7$: C, 61.8; H, 4.3.

Found: 1. C, 62.0; H, 4.4.

2. C, 61.9; H, 4.5.

Trimethyl ester of the A-acid (XII). Eight-tenths gram of the A-acid (XIa) was dissolved in 50 ml. of boiling methanol, the solution quickly cooled, and treated with an ethereal solution of diazomethane. Concentrated to 5 ml., the solution deposited colorless prisms which were twice recrystallized from methanol. The product can be distilled *in vacuo* (14 mm.) without decomposition; m.p. 178–179°.

Anal. Calc'd for $C_{21}H_{24}O_2$: C, 59.7; H, 6.2; CH_3O , 29.4.

Found: C, 59.8, 59.8; H, 6.2, 6.3; CH_3O , 28.7.

Tetramethyl ester (XIII). 1. A solution of 3 g. of the B-acid (XIb) in 60 ml. of methanol was treated with diazomethane, and the crystals (2.5 g.) recrystallized from methanol; long needles, m.p. 208–210°. The substance can be distilled *in vacuo* (14 mm.) without decomposition.

2. On boiling a mixture of the bis-adduct (VIII, 20 g.), methanol (340 ml.), and concentrated sulfuric acid (40 ml.), for four hours, crystals of ester XIII separated (20.5 g.). After recrystallization from methanol, they showed alone and mixed with a sample obtained *via* 1. the m.p. 208–210°.

3. A sample of the ester XIV (see below) was treated with diazomethane; long needles; m.p. alone and mixed with specimens obtained by 1. and 2., 208–210°.

Anal. Calc'd for $C_{21}H_{24}O_6$: C, 59.7; H, 6.2; CH_3O , 29.4.

Found: 1. C, 59.5, 59.7; H, 6.3, 6.4; CH_3O , 29.8.

2. C, 59.8, 59.7; H, 6.2, 6.2.

Trimethyl ester (XIV). A solution of 0.3 g. of the ester XII in 1 ml. of 98% formic acid was boiled a few minutes; on cooling, crystals separated, which were recrystallized from methanol. The substance dissolves in aqueous alkali instantaneously. It gives with diazomethane, ester XIII (see above), m.p. 230–232°.

Anal. Calc'd for $C_{20}H_{24}O_6$: C, 58.8; H, 5.9; CH_3O , 22.8.

Found: C, 58.9; H, 5.8; CH_3O , 23.4.

trans-Keto acid (XV). 1. On boiling 5 g. of the bis-adduct (VIII) with 100 ml. of 5 N hydrochloric acid, slow solution took place. The solution was concentrated at reduced pressure to 20 ml. The crystals were washed with water, recrystallized from water, and dried *in vacuo* at 100°; yield 2.4 g., colorless needles, m.p. 260–262° (dec.).

2. One and seven-tenths grams of the ester XIII was refluxed with 60 ml. of 5 N hydrochloric acid for twelve hours, and the solution was worked up as described in 1.; colorless needles, m.p. alone and mixed with a sample obtained *via* 1., 260–262° (dec.).

3. A solution of 5 g. of the B-acid (XIb) in 50 ml. of hot 5 N hydrochloric acid was refluxed for twelve hours and then worked up as above; m.p. alone and mixed with specimens obtained by 1. and 2., 260–262° (dec.). In mixture with the B-acid (m.p. 265–267°) there was no noteworthy depression of the m.p. to be observed; however, in contrast to the B-acid, the *trans*-keto acid (XV) crystallized unchanged from its solution in acetic anhydride, even when this solution was boiled for a long time.

Anal. Calc'd for $C_{17}H_{16}O_7$: C, 55.7; H, 5.0.

Found: C, 55.4; H, 5.2.

Titration. Calc'd for 4 COOH groups: COOH, 49.2.

Found: COOH, 47.5.

Methyl ester of the trans-keto acid (XV). It was prepared in the customary manner with diazomethane; colorless crystals from methanol, m.p. 154–155°.

Anal. Calc'd for $C_{21}H_{24}O_6$: C, 59.7; H, 6.2.

Found: C, 59.6, 59.5; H, 6.4, 6.5.

Bis-phenylimide of the keto-tetracarboxylic acid (IXb). 1. Three and six-tenths grams of the bis-adduct (VIII) was slowly heated with 8 ml. of freshly-distilled aniline. As the substance dissolved, the reaction became exothermic, and soon crystals began to separate. They were washed with hot ethyl acetate and recrystallized from acetic acid or nitrobenzene; colorless small prisms, which gave negative methoxyl analysis, m.p. 280–285° (dec.).

2. From the anhydride which was prepared by treatment of the B-acid (XIb) with acetic anhydride the same bis-phenylimide was obtained by reaction with aniline.

Anal. Calc'd for $C_{25}H_{24}N_2O_6$: C, 72.5; H, 5.0; N, 5.8.

Found: C, 72.2; H, 5.3; N, 5.8.

Hydropyridazinone derivative (XVI). A solution of 3.7 g. of the B-acid (XIb) and 0.5 g. of phenylhydrazine hydrochloride in 12 ml. of hot water was boiled for five minutes, whereby crystals separated. The product was washed with water, recrystallized from water, and dried *in vacuo* at 100°; colorless needles, m.p. 180°.

Anal. Calc'd for $C_{21}H_{12}N_2O_7$: C, 63.0; H, 5.1; N, 6.4.

Found: C, 62.9, 63.1; H, 5.0, 5.3; N, 6.2.

Titration. Calc'd for one COOH group: COOH, 10.3

Found: COOH, 11.7.

Action of diazomethane on the pyridazinone derivative (XIV). A suspension of 0.1 g. of XVI in 25 ml. of dry methanol was treated with an ethereal solution of diazomethane; colorless needles from xylene, m.p. 295–300° (dec.).

Anal. Calc'd for $C_{25}H_{16}N_2O_7$: C, 64.4; H, 5.6; N, 6.0; CH_2O , 13.3.

Found: C, 64.6, 64.4; H, 5.8, 5.8; N, 6.0; CH_2O , 13.2

Action of hydroxylamine on the B-acid. An aqueous solution of 2 g. of the B-acid (XIb) and 2 g. of hydroxylamine hydrochloride in 5 ml. of hot water was heated on a steam-bath for one hour, whereby crystallization took place. On recrystallization from water, colorless needles were obtained, which were dried in air to constant weight. A tetrahydrate (a) was formed, the crystal water of which was lost by drying *in vacuo* over P_2O_5 at 100° for ten hours; the latter (b), which is sensitive towards moisture, also was obtained by recrystallization of the tetrahydrate from methanol; m.p. 210–211° (dec.).

Anal. Calc'd for $C_{17}H_{19}NO_6 + 4H_2O$: C, 45.4; H, 6.0; for $C_{17}H_{19}NO_6$: C, 53.5; H, 5.0; N, 3.7.

Found. (a) C, 45.4; H, 6.0.

(b) C, 53.4; H, 5.1; N, 3.7

Titration of (a). Calc'd for 2 COOH groups: COOH, 24.4.

Found: COOH, 23.6.

Derivatives of the condensation product described above. 1. By treatment with boiling acetic anhydride, colorless prisms were obtained, m.p. 270–272° (dec.). The substance was neutral and did not liberate CO_2 from a concentrated solution of sodium carbonate. It is probably the acetylated oxime of the bis-anhydride of IXb.

Anal. Calc'd for $C_{19}H_{17}NO_5$: C, 58.9; H, 4.4; N, 3.6.

Found: C, 58.6, 58.5; H, 4.5, 4.8; N, 3.4.

2. Melting led to a resin, which on treatment with acetone gave colorless needles, m.p. 274–275° (dec.).

Anal. Calc'd for $C_{17}H_{15}NO_7$: C, 59.1; H, 4.4; N, 4.1.

Found: C, 58.8, 58.8; H, 4.6, 4.6; N, 4.2, 4.2.

Titration (in acetone solution). Calc'd for 2 COOH groups: COOH, 28.9.

Found: COOH, 26.7.

3. On treatment with diazomethane, colorless prisms were obtained, m.p. 206–208°

Anal. Found: C, 58.9, 58.8; H, 5.9, 5.6; N, 5.0; CH_2O , 24.1.

4. Esterification with dimethyl sulfate led to colorless prisms, m.p. 195°.

Anal. Found: C, 59.3; H, 5.8; N, 5.2, 5.3.

Decomposition of the bis-adduct (VIII) by heating. Four grams of the bis-adduct was placed in a distilling flask and cautiously heated *in vacuo* until distillation began. The oily distillate (3.3 g.) was a mixture containing maleic anhydride and anethole. After the former had crystallized from the oily distillate, it was recrystallized from ethyl acetate, then from benzene; m.p. alone and mixed with an authentic specimen, 54–55°. The oily part of the distillate gave on steam distillation anethole; m.p. alone and mixed with an authentic specimen 21–22°.

3-Methyl-7-methoxynaphthalene-1,2-dicarboxylic acid anhydride. A mixture of 0.35 g. of sulfur and one g. of the bis-adduct (VIII) was heated for fifteen minutes at 230–235° in a metal-bath. After the evolution of hydrogen sulfide stopped, the remainder was extracted with hot ethyl acetate, the solution treated with charcoal, and concentrated to 3 ml. On cooling, red prisms were obtained which gave after two recrystallizations from ethyl acetate yellow needles, the solution of which showed a greenish fluorescence; m.p. 214–217°. The substance was identical with the naphthalene derivative which was obtained by heating a mixture of maleic anhydride and anethole in the manner described in a previous communication (1).

Anal. Calc'd for $C_{14}H_{10}O_4$: C, 69.4; H, 4.2.

Found: C, 69.3; H, 4.3.

The authors wish to acknowledge their indebtedness to Prof. Á. Kiss and Dr. L. Láng for determination of the light-absorption data.

SUMMARY

1. By the action of maleic anhydride on anethole, only a small amount of a crystalline bis-adduct (2:1) could be obtained, the main bulk of the reaction product being a heteropolymer. However, if a small amount of dimethylaniline was added, the formation of the heteropolymer product was prevented, and the yield of the crystalline adduct was high.

2. The correctness of formula IV given earlier for the bis-adduct has been reexamined.

3. If we assume an *endo-cis* type addition, and starting from *trans*-anethole, then the formation of 4 possible stereomers (*i.e.*, 2 racemates) could be expected. All properties of the bis-adduct agree with those expected from VIII (and its mirror image). Therefore we propose as a simpler manner of representation formula IVa instead of the previously used formula IV.

4. The presence and position of the double bond in the condensed ring remains to be established.

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COMPOUNDS FOR CANCER RESEARCH. II.¹ FLUORENE-2-CARBOXAMIDINE

FRANCIS EARL RAY AND PATRICIA QUINLIN

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Several compounds containing the amidino grouping ($-\text{C}:\text{NH}\cdot\text{NH}_2$) have been found to have therapeutic properties. For example, in 1938 Hughes, Lourie, and Yorke (1) found that 1,11-undecanedicarboxamidine had a definite action on human simple tertian malaria, causing the parasites to disappear from the peripheral blood and the febrile paroxysms to cease. Further investigations (2) showed that this and other amidines had a powerful trypanocidal action *in vitro*. Aromatic amidines showed a similar effect (3).

Andrews, King, Van den Ende, and Walker (4) found that *p*-sulfamidobenzamidine (V 147) was much more effective against infections of rickettsia murine and epidemic typhus in mice than was the ester, methyl *p*-sulfonylbenzamidine (V 187). Unfortunately no therapeutic benefit was observed in man. The latter compound, however, proved outstanding in its activity against gas gangrene and haemolytic streptococci.

The amidino group may also be considered to be combined with sulfur in thiourea or with an imino group in guanidine (5). Derivatives of each type have been shown to raise the blood pressure, to increase pulmonary ventilation, and enhance response to adrenalin.

In 1938 Blaschko (6) reported that the enzymatic oxidation of diamines such as putrescine or histamine by extracts of pig's kidney was somewhat inhibited by guanidine. Zeller (7) found that synthalin (decamethylenediguanidine) was a more powerful inhibitor.

In a study of the inhibition of amine oxidase by straight chain amidines Blaschko and Duthie (8) observed the maximum effect when $x = 12$ in $\text{CH}_3(\text{CH}_2)_x\text{C}:\text{NH}\cdot\text{NH}_2$. It will be noted that the optimum has a total of 14 carbon atoms. This fact will be referred to later.

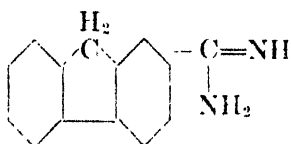
Stilbamidine, $4\text{-NH}_2\cdot\text{NH}:\text{CC}_6\text{H}_4\text{CH}:\text{CHC}_6\text{H}_4\text{C}:\text{NH}\cdot\text{NH}_2\text{-4'}$, has been used with considerable success in the treatment of kala azar, an Indian disease that is characterized by an increase in the globulin content of the serum. Hartwell (12) was led to examine the effects of this compound on tumor bearing mice. He reported that "stilbamidine was active in damaging tumor cells of intramuscular implants of sarcoma 37." In clinical trials Snapper (13) found that "injections of stilbamidine have a favorable influence upon the pains of many patients with multiple myeloma . . . who followed a diet low in protein." In certain types of tissue culture Kopac (14) states that stilbamidine selectively destroyed neoplastic cells from mammary adenocarcinoma R2426 (rat) and transplantable lymphosarcoma (rat).

¹ Part I. Organic Radioiodo Compounds for Cancer Research, Bloch and Ray, *J. Natl. Cancer Inst.*, **7**, 61 (1946).

It seemed profitable, therefore, to join the amidino group with other moieties. To be most effective this group should be combined with a structure that has a known relationship to the cancer cell. Such substances are the carcinogenic hydrocarbons, butter yellow and 2-acetylaminofluorene.

We selected the last named because of its properties of causing cancer in a variety of tissues and at points distant from the site of application, which make it closer in its relationship to natural cancer (9).

It will be seen that fluorene-2-carboxamidine contains 14 carbon atoms; and it will be recalled that Blaschko and Duthie found 14 carbons to give the maximum effect in the aliphatic series (8).



Fluorene-2-carboxamidine

Fluorene was the starting material. It was nitrated, reduced to the amine, diazotized, converted to the cyano derivative, and finally to the amidine. The details will be found in the Experimental Procedure.

Fluorene-2-carboxamidine hydrochloride was obtained in long, light yellow needles from alcohol. It melted at 290° with decomposition and was quite soluble in water but insoluble in ether and benzenes.

The free base was also soluble in alcohol from which light yellow crystals melting at 190° were obtained. It was not appreciably soluble in water but was soluble in organic solvents.

ACKNOWLEDGMENT

Our thanks are due to Dr. C. P. Rhoads for a grant from the Sloan-Kettering Institute for Cancer Research which made this work possible. Both 2-cyanofluorene and fluorene-2-carboxamidine hydrochloride are now under test at the Institute and the results will be reported in a subsequent publication.

EXPERIMENTAL PROCEDURE

2-Nitrofluorene and *2-aminofluorene* were prepared according to the procedure in *Organic Syntheses* (10).

2-Cyanofluorene was prepared by a modification of Fortner's method (11). Dry hydrogen chloride was passed into a solution of 18.1 g. (0.1 *M*) of 2-aminofluorene in 100 cc. of benzene until no further precipitation of 2-aminofluorene hydrochloride occurred. This was filtered and suspended in 25 cc. of concentrated hydrochloric acid, cooled to 0°, and diazotized by adding 6.9 g. of sodium nitrite in a saturated solution until nitrous acid persisted for 10 minutes (starch-iodide paper test). Fluorene-2-diazonium chloride precipitated, was filtered and washed, first with alcohol and finally with ether.

It was suspended in 35 cc. of water and added in small portions to a refluxing solution of 24 g. (0.37 *M*) of potassium cyanide and 22 g. (0.14 *M*) of copper sulfate in 100 cc. of water. After boiling for 1.5 hours, nitrogen evolution ceased and the brown solid was removed by filtration. When dry it was extracted with four 75-cc. portions of ethanol. The alcoholic solution was boiled with 1 g. of charcoal, filtered, and treated with an equal volume of water to precipitate the partially purified 2-cyanofluorene. It now melted at 78°.

After 3 recrystallizations from petroleum ether of boiling point 70-90°, light yellow crystals melting at 92° were obtained. This agrees, substantially, with Fortner's value of 88°.

Anal. Calc'd for $C_{14}H_{11}N$: N, 7.33. Found: N, 7.5, 7.55.

Sometimes when recrystallization was carried out very slowly the melting point obtained was 105°, and the compound was in the form of long, light yellow needles. This is not uncommon in the fluorene series. The analysis and the subsequent reactions showed it to be the same compound, probably a polymorphic crystalline form.

Anal. Calc'd for $C_{14}H_{11}N$: N, 7.33. Found: N, 7.40, 7.36.

The high-melting form of 2-cyanofluorene has not been reported previously.

Fluorene-2-carboxamidine. Dry hydrogen chloride was passed into a suspension of 9.5 g. (0.05 M) of 2-cyanofluorene in 500 cc. of absolute alcohol. Heat was evolved and the solid slowly went into solution. The reaction was maintained at room temperatures by cooling if necessary. A purple solution resulted. After standing for two days, ethyl fluorene-2-imidate hydrochloride had crystallized out. It melted at 135°. A further amount was obtained by evaporating the mother liquor in a current of air.

The solid imino ester was dissolved in 85 cc. of 10% alcoholic ammonia. After 18 hours, fluorene-2-carboxamidine hydrochloride had crystallized out. It melts with decomposition at 290° on the copper block. It was soluble in hot alcohol, sparingly soluble in cold alcohol, but soluble in cold water.

Anal. Calc'd for $C_{14}H_{11}ClN_2$: N, 11.4. Found: N, 11.4, 11.6.

The free base was obtained from the hydrochloride by dissolving the latter in water, filtering if not clear, and adding an excess of 10% sodium hydroxide solution. The fluorene-2-carboxamidine precipitated and was recrystallized from alcohol. It melted at 190° with decomposition. It was not soluble in water but was soluble in organic solvents.

Anal. Calc'd for $C_{14}H_{11}N_2$: N, 13.5. Found: N, 13.3, 13.2.

SUMMARY

The possible therapeutic value of combining the amidino group and the fluorene molecule is discussed and the synthesis of fluorene-2-carboxamidine is described in detail. The results of its use in cancer studies will be reported later.

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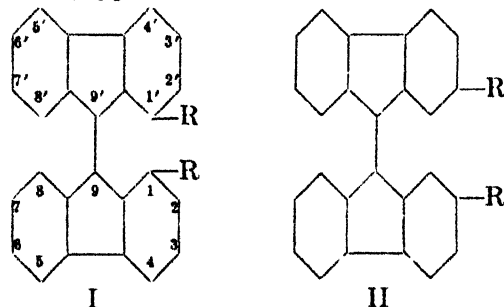
COMPOUNDS FOR CANCER RESEARCH. III. SOME DERIVATIVES OF 9,9'-BIFLUORYL¹FRANCIS EARL RAY, ELIZABETH KREISER WEISBURGER,
AND JOHN H. WEISBURGER*Received April 2, 1948*

Derivatives of fluorene have been found to possess important physiological properties. The amino alcohol esters of fluorene-9-carboxylic acid have local anesthetic and antispasmodic action (1, 2), as do the amino alcohol esters of fluorenone-2-carboxylic acid (3). On the other hand 2-aminofluorene and some of its derivatives have been shown to possess carcinogenic properties (4, 5). Pinck (5) has postulated that carcinogenesis is due to the conversion of the latter compound to a bifluorylidene derivative, which then acts as an intermediate for the elaboration of carcinogens.

Recently compounds substituted with the strongly basic amidino groups $C:NH \cdot NH_2$ have attracted considerable attention owing to their therapeutic activity in several protozoal and bacterial diseases such as leishmaniasis, trypanosomiasis (18), and staphylococcal or streptococcal infections. Straight chain aliphatic compounds carrying terminal amidino groups of the type $H_2N \cdot NH : C - (CH_2)_n - C : NH \cdot NH_2$ were found to exhibit a maximum therapeutic activity when n was equal to 11 (20). Blaschko and Duthie have reported (28) that aliphatic amidines have an inhibiting effect on amine oxidase.

The physiological activity, however, is not confined to the aliphatic series. Aromatic compounds of the type $H_2N \cdot NH : C - C_6H_4 - x - C_6H_4 - C : NH \cdot NH_2$ where x is a simple aliphatic chain, $-(CH_2)_n-$, a chain with ether $-O-(CH_2)_n-O-$ or with ethylenic linkages, as $-CH=CH-$, showed trypanocidal activity (19) and activity against sarcoma 37 in mice (26) and a favorable influence on patients with multiple myeloma (27).

It was therefore of considerable interest to prepare derivatives of 9,9'-bifluoryl substituted symmetrically with amidino groups at the 1,1' positions, type I, and at the 2,2' positions, type II.

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It might be pointed out that in 9,9'-bifluoryl (II), the 2 and 2' positions are separated by 8 carbon atoms. Hence, some physiological activity might be associated with the molecule. The large molecule might be expected to reduce toxic effects.

9,9'-Bifluoryl may be produced by a variety of methods: Action of heat and sodium acetate on a mixture of fluorene and fluorenone (6); amalgamated zinc on 9-chlorofluorene (7); thioacetic acid on 9-chlorofluorene (8); and spontaneous elimination of iodine between two molecules of 9-iodofluorene, the latter being obtained from 9-chlorofluorene and sodium iodide in acetone (9). Bifluoryl also may be obtained by the reduction of 9,9'-bifluorylidene. The latter is formed in the following reactions: The action of heat and chlorine, bromine, or sulfur on fluorene without a solvent (10), or in a solvent (11); copper (12) or silver (13) on 9,9-dichlorofluorene; potassium hydroxide in acetone on 9-chlorofluorene (14); potassium disulfide-potassium hydroxide on 9,9-dichlorofluorene (15); dehydration of 9-fluorylfluorene-9-ol, the latter being derived from a Grignard reaction of 9-fluorylmagnesium bromide on fluorenone (16); and the decomposition of 9-diazo fluorene (17). Despite the fact that there are a number of methods of preparing bifluoryls, only a few derivatives are known.

The starting materials for our syntheses were the well known fluorenone-1- and -2-carboxylic acids. Ray and Kreiser (21) reduced the 9-keto acid to the 9-hydroxy acid with zinc and ammonia in ethanol. Reduction with zinc in aqueous potassium hydroxide, however, resulted in a shorter reaction time and improved yield. Incidentally, an attempt to secure complete reduction of fluorenone-2-carboxylic acid to fluorene-2-carboxylic acid by lengthening the reaction time to eighty-six hours failed.

The 9-chlorofluorene-1- and -2-carbonyl chlorides were obtained from the 9-hydroxy acids by treatment with thionyl chloride and converted into the ethyl esters by reaction with absolute ethanol. The ready preparation of these 9-chloro derivatives suggested the use of Finkelstein's method (9) to join two fluorene nuclei, thereby affording the corresponding bifluoryls.

Attempts to ammonolyze diethyl 9,9'-bifluoryl-1,1'- or 2,2'-dicarboxylate in benzene or ethanol, at room temperature for two months, were unsuccessful. Consequently, the amides were prepared *via* the acids \rightarrow acid chlorides \rightarrow amides. Phosphorus oxychloride then converted the amides into the nitriles in good yields (22).

It was found impossible to prepare diethyl 9,9'-bifluoryl-1,1'-dicarbimide dihydrochloride from 9,9'-bifluoryl-1,1'-dinitrile according to Pinner's method (23). Apparently this nitrile is another ortho substituted nitrile which fails to form an imido ester (24).

9,9'-Bifluoryl-2,2'-dinitrile, however, reacted very readily with absolute ethanol and hydrogen chloride, affording the imido ester, from which 9,9'-bifluoryl-2,2'-dicarboximidine dihydrochloride was prepared in good yields.

This white compound was easily converted to the red 9,9'-bifluorylidene derivative by air oxidation when precipitated from absolute ethanol with ether (small particle size). It was stable to air oxidation when crystallized slowly

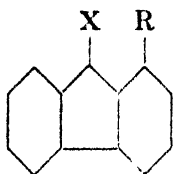
from absolute ethanol (large particle size). A later paper will deal with the bifluorylidene derivatives.

The symmetrically disubstituted bifluoryls should exist in *levo*, *dextro*, and *meso* forms since the 9 and 9' carbons are asymmetric. In this investigation no specific attempt was made to separate the *meso* from the *racemic* form. It was found, however, that after diethyl 9,9'-bifluoryl-1,1'-dicarboxylate had aged for several weeks, recrystallization from ethanol yielded a fraction of m.p. 196–198°. In contrast, the mixture of isomers obtained when this compound was prepared, melted over the range 120–160°. The isomer isolated probably was the racemate. In a similar fashion a high-melting isomer, m.p. 264–267° dec., was separated from the 9,9'-bifluoryl-2,2'-dinitrile mixture, m.p. 110–190°, by recrystallization from acetone and isoamyl alcohol. Ageing of the material seemed to be an important factor, since recrystallization of the compounds shortly after preparation did not result in any definite increase in melting point.

It is of interest to note that the melting points of many bifluoryl derivatives are decomposition points, at which the white bifluoryl compound loses hydrogen and becomes an orange-red bifluorylidene derivative. The latter generally melts to a red liquid. Although these decomposition points are not very sharp, they are nevertheless characteristic of each compound.

In the course of this investigation the following compounds were prepared.

I. Derivatives of the 1,1'-series

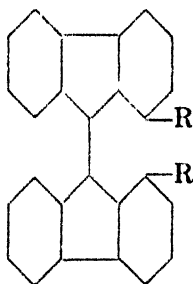


(III), X = =O; R = COOH

(IV), X = OH; R = COOH

(V), X = Cl; R = COCl

(VI), X = Cl; R = COOC₂H₅



(VII), R = COOC₂H₅

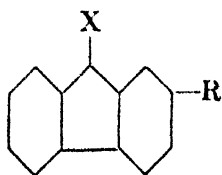
(VIII), R = COOH

(IX), R = COCl

(X), R = CONH₂

(XI), R = CN

II. Derivatives of the 2,2'-series



(XII), X = =O; R = COOH

(XIII), X = OH; R = COOH

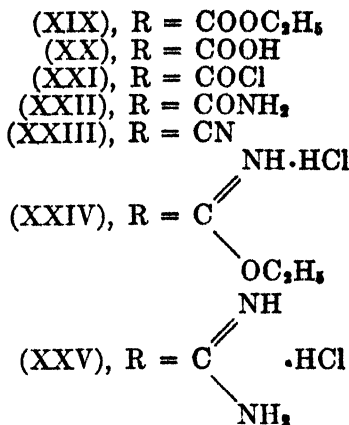
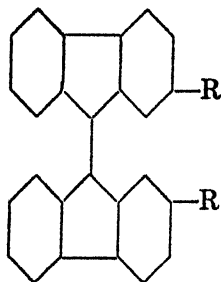
(XIV), X = Cl; R = COCl

(XV), X = Cl; R = COOC₂H₅

(XVI), X = Cl; R = COOCH₃

(XVII), X = Cl; R = CONH₂

(XVIII), X = Cl; R = CN



EXPERIMENTAL

All melting points are uncorrected.

9-Hydroxyfluorene-1-carboxylic acid (IV). A solution of 85 g. of fluorenone-1-carboxylic acid (III) prepared according to Fieser and Seligman (25), in 1700 cc. of water containing potassium hydroxide (97 g.) was heated to 70°. Zinc dust (100 g.) and copper sulfate (0.5 g.) were added. The mechanically stirred mixture was refluxed for two and one-half hours and the excess zinc then filtered off. The resulting cold, tan solution was neutralized dropwise with dilute hydrochloric acid while stirred mechanically over a period of three hours. Rapid addition of acid tends to produce gums. The pinkish-white acid was filtered, washed and oven-dried at 115°. The yield of acid melting at 191–194° was 80 g. (94%). A sample recrystallized twice from xylene was creamy-white, m.p. 198–199°.

Anal. Calc'd for C₁₄H₁₀O₂: C, 74.3; H, 4.45.

Found: C, 74.53; H, 4.43.

9-Chlorofluorene-1-carbonyl chloride (V). 9-Hydroxyfluorene-1-carboxylic acid (50 g.) was refluxed with thionyl chloride (250 cc.) until complete solution was effected. The solution was allowed to stand overnight, affording a crop of crystals, m.p. 162–163°, after filtering and washing with ligroin (30–60°).

Anal. Calc'd for C₁₄H₉Cl₂O: Cl, 27.0. Found: Cl, 25.92, 26.05.

Evaporation of the thionyl chloride filtrate yielded a further crop of crystals. This material was washed with ligroin and used in the next step.

Ethyl 9-chlorofluorene-1-carboxylate (VI). The combined fractions of the acid chloride (V) were heated on a water-bath with absolute ethanol (300 cc.) until all material had dissolved. The ethanol was distilled off, leaving the ester as a dark oil. This was refluxed with two 300-cc. portions of ligroin (30–60°), which were decanted from the oil after one-half hour. The ligroin solution was clarified with Darco and allowed to stand in an ice-bath overnight. A crop of long white needles, weighing 44 g. (73%), was obtained.

A sample recrystallized again from ligroin (30–60°) melted at 56–57°.

Anal. Calc'd for C₁₆H₁₃ClO₂: Cl, 13.0. Found: Cl, 12.83, 13.05.

Diethyl 9,9'-bifluorenyl-1,1'-dicarboxylate (VII). Ethyl 9-chlorofluorene-1-carboxylate (50 g.) in acetone (100 cc.) was added to sodium iodide (65 g.) in acetone (400 cc.). After a few seconds, iodine was liberated and sodium chloride precipitated. The mixture was refluxed for one-fourth hour and allowed to stand overnight. A solution of sodium hydrogen sulfite (50 g.) in 350 cc. of water was added with mechanical stirring to reduce the iodine and precipitate the ester. After stirring the suspension for five minutes, water was added to make a total volume of two and one-half liters, and stirring then continued for one-fourth hour. When the precipitate had settled, it was filtered and washed. The yield of creamy white material, m.p. 120–160°, was 41 g. (95%). A sample recrystallized from ethanol

melted at 130–160°. Upon ageing for four weeks, a sample recrystallized again from ethanol melted at 196–198°.

Anal. Calc'd for $C_{12}H_{10}O_4$: C, 81.2; H, 5.5.

Found: C, 80.50, 80.50; H, 5.57, 5.48.

9,9'-Bifluoryl-1,1'-dicarboxylic acid (VIII). The crude ester (VII) (40 g.) was suspended in ethanol (500 cc.) containing potassium hydroxide (11 g.) and refluxed on a water-bath for two hours. Then water (1000 cc.) was added and the suspension heated to near boiling. After filtration, the mechanically stirred yellowish filtrate was acidified at the boiling point. The precipitate was allowed to stand overnight, filtered, and washed. After solution in hot sodium hydrogen carbonate and reprecipitation with dilute hydrochloric acid, 31.5 g. of a white material, m.p. 340° (block) was obtained.

Anal. Calc'd for $C_{12}H_{10}O_4$: C, 80.5; H, 4.32.

Found: C, 79.93, 79.85; H, 4.51, 4.37.

9,9'-Bifluoryl-1,1'-dicarbonyl chloride (IX). The acid (VIII) (27 g.) was refluxed with thionyl chloride (250 cc.) until dissolved. Upon standing overnight the acid chloride crystallized out. After filtering and washing with ligroin (30–60°), 17 g. of white needles, m.p. 272–275° dec. were obtained.

Anal. Calc'd for $C_{12}H_{10}Cl_2O_2$: Cl, 15.6. Found: Cl, 14.63, 14.67.

A less pure material, used in the next step, was obtained from the thionyl chloride filtrate.

9,9'-Bifluoryl-1,1'-dicarboxamide (X). The acid chloride (IX) was treated with ice-cold concentrated ammonium hydroxide (100 cc.). After standing for one hour, 12 g. of light tan amide, m.p. >310° was obtained.

The crystalline acid chloride (IX) (10 g.) similarly yielded 8 g. of analytically pure amide (m.p. >310°). The amide is sparingly soluble in the usual organic solvents.

Anal. Calc'd for $C_{12}H_{12}N_2O_2$: N, 6.73. Found: N, 6.89, 6.83.

9,9'-Bifluoryl-1,1'-dinitrile (XI). The amide (X) (9.5 g.) was added to phosphorus oxychloride (50 cc.). On heating slowly, hydrogen chloride was evolved between 40° and 70°, and the amide dissolved. The solution was refluxed for $\frac{1}{2}$ hour and added with mechanical stirring in small portions to 100 cc. of water. Additions of ice kept the temperature between 35 and 50°. After hydrolysis of the phosphorus oxychloride, the mixture was cooled to 15–20° and stirred for $\frac{1}{2}$ hour. The precipitated nitrile was filtered and washed, yielding a greyish-white, felt-like material (9.5 g.) beginning to melt and decompose at 300°. After two crystallizations from dioxane, the small white needles melted at 328° (block).

Anal. Calc'd for $C_{12}H_{10}N_2$: N, 7.36. Found: N, 7.20; 7.21.

9-Hydroxyfluorene-2-carboxylic acid (XIII). Fluorenone-2-carboxylic acid (3) (XII) (125 g.) was reduced with zinc dust (150 g.) activated with copper sulfate (0.5 g.) in water (2500 cc.) containing potassium hydroxide (140 g.) as described for the 1-isomer (III). The hydroxy acid does not show the tendency to produce gums as the 1-isomer does. It may be precipitated easily from alkaline solution with concentrated hydrochloric acid; yield 105 g. (84%), m.p. 237° (block). One recrystallization from ethanol raised the m.p. to 240° (block) as reported by Ray and Kreiser (21).

9-Chlorofluorene-2-carbonyl chloride (XIV). The acid (XIII) (100 g.) was refluxed with thionyl chloride (450 cc.) for one hour, yielding a brown solution. Thionyl chloride (200 cc.) was distilled off and the remaining solution allowed to stand overnight. The precipitated crystals were filtered and washed with ligroin (30–60°) until white; 63 g., m.p. 136–150°.

Anal. Calc'd for $C_{14}H_9ClO$: Cl, 27.0. Found: Cl, 26.4.

The thionyl chloride filtrate was distilled to dryness on a water-bath and the residue washed with ligroin (30–60°), yielding another 45 g. of material.

Ethyl 9-chlorofluorene-2-carboxylate (XV). The crystalline acid chloride (63 g.) obtained above was refluxed with absolute ethanol (400 cc.) for one hour. The mixture was chilled and allowed to stand for two hours. The precipitated ester was filtered and washed with absolute ethanol. After air-drying, the white solid weighed 65 g. and melted at 127–128°.

The filtrate was added to the 45 g. of the less pure acid chloride. After identical treatment, a tan material (m.p. 120–125°) resulted. Recrystallized from ligroin (90–120°) (Darco) it yielded 40 g. of light tan ester, m.p. 126–128°. A sample recrystallized twice from ligroin (90–120°) melted at 128–129°.

Anal. Calc'd for $C_{15}H_{11}ClO_2$: Cl, 13.0. Found: Cl, 12.9.

Methyl 9-chlorofluorene-2-carboxylate (XVI). The acid chloride (XIV), treated with absolute methanol as described for the ethyl ester, afforded white crystals m.p. 107–109°, which when recrystallized from ligroin (60–90°) formed tiny needles, m.p. 110–111°.

Anal. Calc'd for $C_{16}H_{11}ClO_2$: Cl, 13.71. Found: Cl, 13.55.

9-Chlorofluorene-2-carboxamide (XVII). The acid chloride (XIV) (26 g.) stirred with ice-cold concentrated ammonium hydroxide (300 cc.) for one hour yielded 23.5 g. (97%) of white material, m.p. 227° dec. A sample recrystallized from isoamyl alcohol melted at 227–228° dec.

Anal. Calc'd for $C_{15}H_9ClNO$: N, 5.76. Found: N, 5.66.

9-Chlorofluorene-2-nitrile (XVIII). The amide (XVII) (2 g.) was treated with phosphorus oxychloride (20 cc.) as described for X. A light tan material (1.7 g.), m.p. 156–159° was obtained. When recrystallized from isoamyl alcohol (Darco), it formed small white needles, m.p. 158–159°.

Anal. Calc'd for $C_{15}H_7ClN$: N, 6.22. Found: N, 6.13.

Diethyl 9,9'-bifluoryl-2,2'-dicarboxylate (XIX). Sodium iodide (130 g.) in acetone (820 cc.) was added to ethyl 9-chlorofluorene-2-carboxylate (XV) (100 g.) in acetone (500 cc.) and the reaction carried out as for the 1,1'-isomer (VII). The yellowish white crude product (90 g.) melted with decomposition at about 200°.

Six grams of the crude material, when recrystallized three times from xylene, yielded 1.8 g. of white crystals, starting to melt partially at 220°; at 227° the melt reddens and the last crystals disappear at 245°.

Anal. Calc'd for $C_{22}H_{16}O_4$: C, 81.2; H, 5.5.

Found: C, 80.83; H, 5.49.

9,9'-Bifluoryl-2,2'-dicarboxylic acid (XX). The ester (XIX) (84 g.) was saponified with 23.6 g. of potassium hydroxide in 500 cc. ethanol as described for the 1,1'-isomer (VII), except that the acid as precipitated from the alkaline solution was digested on a steam-bath for five hours and allowed to stand overnight to facilitate filtration (the acid precipitates in very fine particles). Purification by reprecipitation from sodium hydrogen carbonate solution was omitted, except for a small amount used as an analytical sample. The acid is insoluble in the usual organic solvents; yield 72 g. (97%), m.p. >360°.

Anal. Calc'd for $C_{22}H_{14}O_4$: C, 80.5; H, 4.32.

Found: C, 79.46; H, 4.51.

9,9'-Bifluoryl-2,2'-dicarbonyl chloride (XXI). The acid (XX) (65 g.) yielded a brown solution when refluxed for six hours with thionyl chloride (600 cc.). The solution was allowed to stand overnight after distilling off 300 cc. of thionyl chloride. The resulting crystals, after filtering and washing with ligroin (30–60°) weighed 28.5 g. and melted at 284–288° dec.

Anal. Calc'd for $C_{22}H_{10}Cl_2O_2$: Cl, 15.6. Found: Cl, 14.76, 14.79.

The mother liquor distilled down to 100 cc. was diluted with 400 cc. of ligroin (30–60°), affording another 35 g. of material.

9,9'-Bifluoryl-2,2'-dicarboxamide (XXII). The acid chloride (XXI) (61 g.) was added to ice-cold concentrated ammonium hydroxide (700 cc.), stirring being maintained for one hour. After filtering and washing, 65 g. of a greyish-white material was obtained. It was very slightly soluble in hot dioxane or hot isoamyl alcohol. A sample was recrystallized from glacial acetic acid-water, yielding a white product which turns red on a copper block at 360°.

Anal. Calc'd for $C_{22}H_{18}N_2O_2$: N, 6.73. Found: N, 6.67.

An identical product was obtained as follows: A solution of sodium iodide (35 g.) in acetone (350 cc.) was added to a suspension of 9-chlorofluorene-2-carboxamide (XVII) (23

g.) in acetone (330 cc.). The mixture was refluxed on a water-bath for $\frac{1}{2}$ hour, iodine being liberated. After standing for twenty-four hours, the volume was reduced to 500 cc. To the cold, brown mixture a solution of sodium hydrogen sulfite (10 g.) in water (1200 cc.) was added in portions with stirring. The light yellow suspension was stirred for $\frac{1}{2}$ hour, filtered, and washed. The yellow material (20 g.), melting from 300° upward with decomposition, contained some free iodine. A small sample recrystallized from acetic acid-water, as before, gave the white amide.

9,9'-Bifluoryl-2,2'-dinitrile (XXIII). The amide (XXII) (65 g.) was treated with phosphorus oxychloride (200 cc.) as described for the 1,1'-isomer (XI). A crude yield of 62 g. of grey-tan material, shrinking around 90° and forming a pasty brown mass from 110° upward, was obtained. *Separation of isomers.* The crude material was dissolved in 300 cc. of acetone, boiled with Darco for $\frac{1}{2}$ hour, and filtered. The filtrate was reduced to 200 cc. and allowed to stand overnight. After filtering off the crystals and washing with five 20-cc. portions of acetone, a second crop was obtained by evaporating the mother liquor to 100 cc. The two solid fractions were combined (21.8 g.) and extracted with a limited amount of acetone (125 cc.), affording 12 g. of a granular white material (A), m.p. 215–235°. The combined acetone mother liquors were evaporated. The resulting dark oil was refluxed with 300 cc. of isoamyl alcohol, clarified with Darco, and cooled to allow crystallization. After filtration and evaporation of the filtrate, a total amount of 24.5 g. of material (B), m.p. 110–140° was obtained.

After ageing for four weeks, a sample of material (A) recrystallized three times from isoamyl alcohol formed beautiful white needles, m.p. 264–267° dec.

Anal. Calc'd for $C_{22}H_{16}N_2$: N, 7.36. Found: N, 7.39, 7.44.

A sample of material (B) recrystallized twice from isoamyl alcohol formed light tan granular crystals, m.p. 110–135° dec.

Anal. Calc'd for $C_{22}H_{16}N_2$: N, 7.36. Found: N, 7.20.

Diethyl 9,9'-bifluoryl-2,2'-dicarbimidate dihydrochloride (XXIV). 9,9'-Bifluoryl-2,2'-dinitrile (XXIII) (6 g.) was dissolved in absolute dioxane (50 cc.). Absolute ethanol (5 cc.) was added and the solution cooled in an ice-salt bath. Dry hydrogen chloride was bubbled in until the solution was saturated. The flask was stoppered and allowed to stand at room temperature for twenty-eight hours. The resulting crystals were filtered and washed with peroxide-free anhydrous ether. The white material melted on a copper block with decomposition around 215°. In a capillary only a progressive shrinking was noted from 180° upwards (decomposition into amide and ethyl chloride).

Anal. Calc'd for $C_{22}H_{16}Cl_2N_2O_2$: N, 5.13. Found: N, 4.75.

An additional amount was recovered by diluting the filtrate with 150 cc. of anhydrous ether.

9,9'-Bifluoryl-2,2'-dicarboxamidine dihydrochloride (XXV). Absolute ethanol (150 cc.) saturated at 0° with ammonia was added to the imido ester (XXIV). A light yellow solution was formed after standing for sixty hours. It was filtered and reduced *in vacuo* to 50 cc. The white crystalline precipitate thus formed was filtered, washed with small amounts of absolute ethanol and ether and dried in a vacuum desiccator. It weighed 4.0 g. The filtrate was reduced to 20 cc. and diluted with 100 cc. of peroxide-free ether. The precipitate was filtered and washed with ether, taking care to keep the solid covered with liquid. The ether was allowed to evaporate slowly in a large desiccator, leaving 2.9 g. of cream-white, soft material. The total yield was 6.9 g. or 90%. The salt is freely soluble in water or 95% ethanol. The finely divided material was very sensitive to air oxidation. Moisture and ether peroxides probably catalyzed the oxidation. In one run, where no particular precautions were taken, the white 9,9'-bifluoryl derivative was oxidized quantitatively to the red 9,9'-bifluorylidene. Crystallization from 6 N hydrochloric acid also yielded the bifluorylidene. Crystallization in the presence of zinc dust prevented the oxidation.

A sample recrystallized from absolute ethanol-ether shrank around 270°, deepening in color from white to orange to red and finally starting to melt at 310°.

Anal. Calc'd for $C_{20}H_{14}Cl_2N_4$: N, 11.50. Found: N, 11.32, 11.13.

SUMMARY

In the search for substances of possible physiological activity, a number of symmetrically disubstituted derivatives of 9,9'-bifluoryl have been prepared. These include 9,9'-bifluoryl-1,1'-dinitrile and intermediates, and 9,9'-bifluoryl-2,2'-dicarboxamidine dihydrochloride and intermediates.

CINCINNATI 21, OHIO.

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SOME REACTIONS OF ISOAMIDONE

EVERETTE L. MAY AND ERICH MOSETTIG

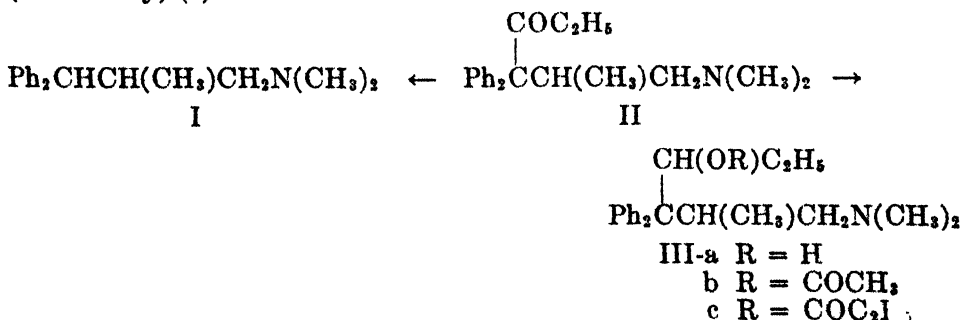
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In a preceding publication (1) we reported that amidone (6-dimethylamino-4,4-diphenyl-3-heptanone), while resistant to reduction with aluminum isopropoxide or sodium amalgam, and to hydrogenation with Raney nickel, could be hydrogenated to the carbinol with platinum oxide. The O-acetyl and O-propionyl derivatives of this carbinol were found to have favorable analgesic properties, comparable to amidone. These investigations have now been extended to include the synthesis and pharmacological study of analogous acyl derivatives of 6-dimethylamino-4,4-diphenyl-5-methyl-3-hexanol (III-a).

Unlike amidone, isoamidone (6-dimethylamino-4,4-diphenyl-5-methyl-3-hexanone) (II) did not absorb hydrogen in the presence of platinum oxide. Reduction to the carbinol III-a was ultimately achieved with lithium aluminum hydride, the excellent new reagent discovered by Finholt, Bond, and Schlesinger (2).¹ Likewise, amidone was converted to the corresponding carbinol more advantageously than with platinum oxide. In each instance, only one of the two possible diastereoisomers was encountered. Acylation of III-a to III-b and III-c was accomplished with acetic or propionic anhydride by the method of Houben (4) as described for 6-dimethylamino-4,4-diphenyl-3-heptanol (1).

Alkaline cleavage of the ethyl keto group of isoamidone did not proceed as readily as with amidone. After prolonged reaction, a product was obtained for which we postulate, by analogy (1) and on the basis of analytical data, the formula of 3-dimethylamino-1,1-diphenyl-2-methylpropane (I). The isolation of I was initially complicated by the fact that the picrates of I and II form a double compound, separable into its basic components *via* the hydrochloride salts. This difficulty was subsequently obviated by prolonging the reaction time and isolation of I as the hydrochloride rather than as the picrate salt.

Conversion of isoamidone to the carbinol III-a results in an almost complete loss of analgesic effect. Acetylation and propionylation of the hydroxyl group restore activity to one-half and one-fourth, respectively, that of isoamidone (N. B. Eddy) (5).



¹ Cf. Nystrom and Brown (3).

EXPERIMENTAL^{2,3}

6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanol (III-a). To 10 ml. of 1.4 *M* lithium aluminum hydride in ether and 25 ml. of dry ether was added during 15–20 minutes (stirring) the base of II (from 5 g. of hydrochloride)⁴ in 50 ml. of dry ether. After another one-half hour, 10 ml. of water was added dropwise and the mixture stirred for ten minutes. The dried, ethereal solution was evaporated to dryness and the residue crystallized from ligroin (30–60°) to give 3.5 g. (75%) of prisms, m.p. 102–104°. They could be sublimed, or recrystallized from aqueous ethanol; m.p. 103–104.5°.

Anal. Calc'd for $C_{21}H_{29}NO$: C, 80.9; H, 9.4.

Found: C, 80.7; H, 9.3.

Similarly, amidone was reduced to the carbinol, which was isolated from aqueous ethanol in a yield of 90%, m.p. 100–101°. A mixture with carbinol described previously (1) had the same m.p.

The hydrochloride of III-a crystallized from acetone-ether in needles, m.p. 198–200°.

Anal. Calc'd for $C_{21}H_{29}ClNO$: C, 72.5; H, 8.7.

Found: C, 72.4; H, 8.7.

3-Acetoxy-6-dimethylamino-4,4-diphenyl-5-methylhexane (III-b) hydrochloride. To a stirred, ice-cooled solution of 1.5 g. of III-a in 20 ml. of dry ether was added slowly 18 ml. of 0.6 *M* ethereal ethylmagnesium bromide, then 1.5 ml. of acetic anhydride in 20 ml. of dry ether during five minutes. The mixture was refluxed for thirty minutes, shaken overnight, and stirred while adding slowly 10–20 ml. of water and 5 ml. of 10% potassium hydroxide. The ether was dried and acidified with 1.7 ml. of 15% alcoholic HCl to give 1.8 g. (95%) of hydrochloride, m.p. 129–132°. It crystallized from acetone-ether in plates (m.p. 129–132°)⁵ or prisms, m.p. 220–222° (dec.). The prisms were analyzed.

Anal. Calc'd for $C_{23}H_{33}ClNO_2$: C, 70.8; H, 8.3.

Found: C, 70.6; H, 8.0.

The picrate, prepared from either the plates or the prisms with ethanolic picric acid, melted at 223–224° (dec.); yellow prisms.

Anal. Calc'd for $C_{29}H_{41}N_4O_8$: C, 59.8; H, 5.9.

Found: C, 60.1; H, 6.1.

6-Dimethylamino-4,4-diphenyl-5-methyl-3-propionyxyhexane (III-c) picrate. The foregoing experiment was repeated (2 ml. of propionic anhydride). The dried ether layer, in this case, was evaporated to dryness and the base, in ethanol, was treated with 1.5 g. of picric acid in ethanol to give 2.5 g. (85%) of picrate, m.p. 213–214°, yellow prisms from acetone-alcohol.

Anal. Calc'd for $C_{30}H_{38}N_4O_8$: C, 60.4; H, 6.1.

Found: C, 60.4; H, 6.2.

The hydrochloride crystallized from acetone-ether in prisms, m.p. 197–199°.

Anal. Calc'd for $C_{24}H_{34}ClNO_2$: C, 71.4; H, 8.5.

Found: C, 71.2; H, 8.7.

3-Dimethylamino-1,1-diphenyl-2-methylpropane (I) hydrochloride. A mixture of 2.0 g. of II hydrochloride, 1.6 g. of potassium hydroxide, and 10 ml. of triethylene glycol was refluxed (bath temperature 220–230°) for 11–16 hours. Water and ether were added and the ether layer was dried and acidified with 2 ml. of alcoholic HCl. The oily hydrochloride crystallized from acetone-ether or ethyl acetate in prisms of m.p. 182–184°; yield 0.6–0.8 g. (35–50%).

² All melting points given are uncorrected.

³ The microanalyses are from the Institute service analytical laboratory under the direction of C. A. Kinser.

⁴ This material was generously supplied by the Mallinckrodt Chemical Works.

⁵ If the temperature rise is very slow from 120–130°, the plates merely sinter at 130° and melt at 220–222° (dec.). The plates are converted to the prisms either by recrystallization or by grinding.

Anal. Calc'd for $C_{13}H_{14}ClN$: C, 74.6; H, 8.4.

Found: C, 74.5; H, 8.3.

The picrate crystallized from ethanol in yellow prisms, m.p. 157.5–159°.

Anal. Calc'd for $C_{24}H_{24}N_4O_7$: C, 59.7; H, 5.4.

Found: C, 59.9; H, 5.4.

Double compound of the picrates of I and II. When the above reaction was carried out for 4–6 hours, an 80% yield of picrate of m.p. 169–171° was isolated. The same picrate was obtained on recrystallization (ethanol) of approximately equimolar amounts of the picrates of I and II.

Anal. Calc'd for $C_{27}H_{26}N_4O_8 \cdot C_{24}H_{24}N_4O_7$: C, 60.0; H, 5.5.

Found: C, 59.9; H, 5.5.

The double compound was converted to the bases (aqueous ammonia-ether). Fractional crystallization of the hydrochlorides of these basic products gave almost equal amounts of the hydrochlorides of I and II. Furthermore, the bases prepared from the double compound gave, as described above (alkali, triethylene glycol, 225°, ten hours), pure I hydrochloride in a yield of 50%.

SUMMARY

The reduction of isoamidone and amidone to the corresponding carbinols has been effected with lithium aluminum hydride.

Treatment of isoamidone in triethylene glycol with alkali at 220–230° gives 3-dimethylamino-1,1-diphenyl-2-methylpropane.

3-Acetoxy-6-dimethylamino-4,4-diphenyl-5-methylhexane and the propionoxy homolog have been prepared and evaluated as analgesic agents.

BETHESDA 14, Md.

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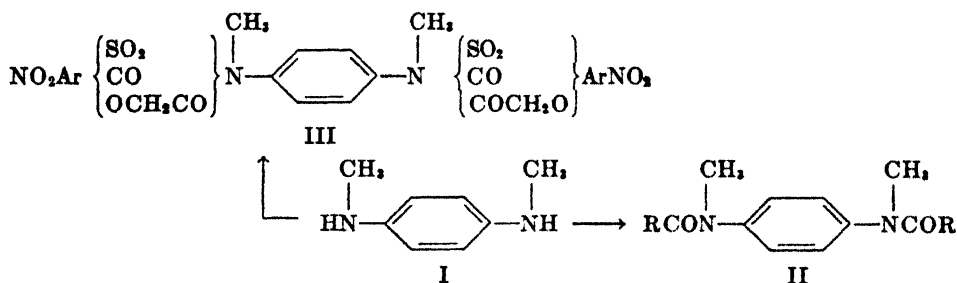
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CERTAIN DERIVATIVES OF *sym.*-DIMETHYL-*p*-PHENYLENEDIAMINEC. F. H. ALLEN, J. V. CRAWFORD, G. F. FRAME, J. E. JONES, E. R. WEBSTER,
AND C. V. WILSON

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sym.-Dimethyl-*p*-phenylenediamine (I) can be converted by relatively simple reactions into amines which can be tetrazotized and transformed into azo dyes, and into surface-active substances such as *bis*-quaternary salts, and *bis*-acyl derivatives.

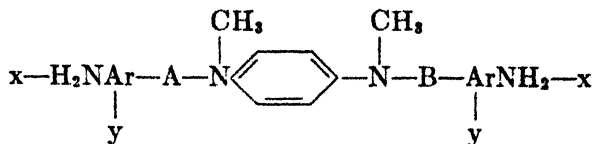
For instance, it is easily acylated, the nature of the product depending upon the acyl halide selected. Dipalmitoyl and distearoyl derivatives (II; R = C₁₅H₃₁, C₁₇H₃₅) result when palmitoyl and stearoyl chlorides are used. Of more



interest are the chlorides of nitrated aromatic carboxylic or sulfonic acids, which give rise to nitro derivatives (III), the reduction of which leads to diazotizable amines, and, hence, to azo dyes. The use of the acid chlorides of halogenated aliphatic acids (*e.g.*, chloroacetyl chloride) furnishes a means of preparing *bis*-quaternary salts with bases, some of which have surface-active properties. A variation in the acid chloride is 2,4-dinitrochlorobenzene; selective reduction of the product of the reaction leads to a diamine, which can be used for preparing azo dyes.

The following nitrated aromatic acid chlorides have been used: *p*-nitrobenzoyl-; *m*- and *p*-nitrobenzenesulfonyl-; 2-sulfo-4-nitrobenzoyl-; 4-nitrophenoxyacetyl-; and 1-nitro-2-naphthoxyacetyl-.

The corresponding amines (IV) were prepared by catalytic reduction of the nitro compounds, using Raney nickel. In the general formula, A and B represent the linkages between the aromatic ring, Ar, and the nitrogen of the phenyl-



IV

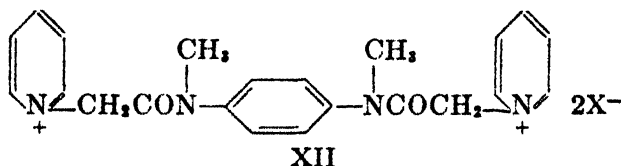
enediamine, and x is the position of the amino group (y is any other substituent; unless otherwise indicated, it represents hydrogen).

A list of the amines is as follows:

- V. 1,4-*bis*-(4'-Aminobenzoyl-*N*-methylamino)benzene; A, B = CO; $x = 4$;
Ar = C₆H₄
- VI. 1,4-*bis*-(3'-Aminobenzenesulfonyl-*N*-methylamino)benzene; A, B = SO₂;
 $x = 3$; Ar = C₆H₄
- VII. 1,4-*bis*-(4'-Aminobenzenesulfonyl-*N*-methylamino)benzene; A, B = SO₂;
 $x = 4$; Ar = C₆H₄
- VIII. 1,4-*bis*-(4'-Amino-2'-sulfo benzoyl-*N*-methylamino)benzene; A, B = CO;
 $x = 4$; $y = 2$ (SO₂H); Ar = C₆H₄
- IX. 1,4-*bis*-(4'-Aminophenoxyacetyl-*N*-methylamino)benzene; A = OCH₂-
CO; B = COCH₂O; $x = 4$; Ar = C₆H₄
- X. 1,4-*bis*-(1'-Amino-2'-naphthoxyacetyl-*N*-methylamino)benzene; A =
OCH₂CO; B = COCH₂O; $x = 1'$; Ar = C₁₀H₆
- XI. 1,4-*bis*-[4'(or 2')-Amino-2'(or 4')-nitrophenyl-*N*-methylamino]benzene;
no A; $x = 4'$ (or $2'$); $y = 2'$ (or $4'$)

Azo dyes were subsequently prepared from the *bis*-diamines and the usual benzene and naphthalene dye intermediates. Those obtained from sulfonic acids dyed wool directly; those from J acid dyed both wool and cotton; while those without sulfonic acid groups colored cellulose acetate. The dyes formed are summarized in Table I, which shows the amine used, the coupling component, and the color of the dyed fabric. Mixed disazo, trisazo, and tetrakisazo dyes were also prepared. The most brilliant colors resulted when the aminophenoxyacetyl derivative (IX) was used.

The *bis*-quaternary salt shown in Formula XII ($X = \text{Cl}$) was obtained by



treating the *sym*-dimethyl-*p*-phenylenediamine with two equivalents of chloroacetyl chloride, followed by addition of the *bis*-halide (II; R = ClCH₂) thus formed to pyridine.

EXPERIMENTAL

Acylation. *N,N'*-Dimethyl-*p*-phenylenediamine was isolated as the solid oxalate; this salt was used in most operations, the free base being liberated by alkali. In some instances when the absence of water was essential, the free base was extracted with ether.

N,N'-Distearoyl-*N,N'*-dimethyl-*p*-phenylenediamine (II; R = C₁₇H₃₅). To a suspension of 3.2 g. of the oxalate of *N,N'*-dimethyl-*p*-phenylenediamine in sodium hydroxide solution (4 g. of the solid dissolved in 50 ml. of water) 6.7 g. of stearoyl chloride was added over a period of one-half hour. The reaction mixture became very viscous. The purplish solid was then triturated with alcohol and separated by filtration. It was twice recrystallized from acetone; the yield was 52%; it melted at 77-79°.

N,N'-Dipalmitoyl-*N,N'*-dimethyl-*p*-phenylenediamine (II; R = C₁₅H₃₁) was similarly prepared in a yield of 73.5%, and recrystallized from pyridine. It melted at 88-90°.

Anal. Calc'd for $C_{40}H_{72}N_2O_2$: C, 78.4; H, 11.8.
Found: C, 78.5; H, 11.9.

TABLE I
SYMMETRICAL DISAZO DYES

AMINE USED	COUPLING COMPONENT	COLOR OF DYE FORMED	
		ON WOOL	OTHER FIBER ^a
V	1-Hydroxynaphthalene-5-SO ₃ H	Red-orange	
V	2-Hydroxynaphthalene-7-SO ₃ H	Orange	
V	1-Hydroxynaphthalene-3,6-diSO ₃ H	Red-orange	
V	1-Hydroxynaphthalene-3,8-diSO ₃ H	Red-orange	
V	2-Hydroxynaphthalene-3,6-diSO ₃ H	Scarlet	
V	2-Hydroxynaphthalene-6,8-diSO ₃ H	Orange	
V	1,8-Dihydroxynaphthalene-3,6-diSO ₃ H	Dull magenta	
V	1-Amino-8-hydroxynaphthalene-2,4-diSO ₃ H	Magenta	
V	1-Amino-8-hydroxynaphthalene-3,6-diSO ₃ H	Dull magenta	
V	1-Acetamino-8-hydroxynaphthalene-3,6-diSO ₃ H	Rose	
V	2-Amino-5-hydroxynaphthalene-7-SO ₃ H	Orange	Old rose, C ^c
V	2-Benzamido-5-hydroxynaphthalene-7-SO ₃ H	Red-orange	Red-orange, C
V	2-Amino-8-hydroxynaphthalene-6-SO ₃ H	Maroon	
V	2-Amino-8-hydroxynaphthalene-3,6-diSO ₃ H	Maroon	
V	N-Ethyl-N-β-hydroxyethylaniline		Yellow, CA
V	N,N-Di-[β-hydroxyethyl] aniline		Yellow, CA
V	7-Methyl-1-glyceryl-1,2,3,4-tetrahydroquinoline ^b		Red, CA
VI	1-Hydroxynaphthalene-4-SO ₃ H	Orange	
VI	1-Amino-8-hydroxynaphthalene-2,4-diSO ₃ H	Maroon	
VI	5-Hydroxy-1-glycerylaminonaphthalene ^b		Violet, CA
VII	4-Acetamino-2-glycerylaminoanisole ^b		Salmon, CA
IX	1-Hydroxynaphthalene-4-SO ₃ H	Carmine	
IX	1-Amino-8-hydroxynaphthalene-2,4-diSO ₃ H	Violet	
X	1-Amino-8-hydroxynaphthalene-2,4-diSO ₃ H	Brown-violet	
XI	5-Hydroxy-1-glycerylaminonaphthalene ^b		Red-violet, CA

^a C = cotton; CA = cellulose acetate. ^b Glyceryl = 2,3-dihydroxypropyl.

TABLE II
ANALYSES FOR NITROGEN

AMINE	EMPIRICAL FORMULA	CALC'D, %	FOUND, %
V	$C_{22}H_{22}N_4O_2$	14.9	14.5
VI	$C_{20}H_{12}N_4O_4S_2$	12.6	12.6
IX	$C_{24}H_{24}N_4O_4$	12.9	12.8

These two derivatives are softening agents for textiles. Analogous products are mentioned in a patent (1) as being water-repellent, but no examples are given.

N,N'-Dichloroacetyl-*N,N'*-dimethyl-*p*-phenylenediamine (II; R = ClCH₂). To a suspension of 31.6 g. of the diamine oxalate in 42.4 g. of sodium carbonate and 300 ml. of water was added gradually 40 g. of chloroacetyl chloride. The mixture was stirred for an addi-

tional two hours, and the product separated by filtration. The yield was 30 g. It was recrystallized from acetic acid; the pink crystals melted at 190°, with decomposition.

N,N'-Di-*S'*-chloroacetylaminobenzenesulfonyl-*N,N'*-dimethyl-*p*-phenylenediamine (IV; A = SO₂, Ar = C₆H₄, x = 3) was prepared from a solution of 4 g. of the diamine, VI, in 100 ml. of dioxane, to which was added 1 g. of solid sodium carbonate, followed by 5 g. of chloroacetyl chloride, dropwise. The solid product was removed after three hours and recrystallized from acetic acid. It melted at 184°.

Anal. Calc'd for C₂₄H₂₄Cl₂N₄O₆S₂: N, 9.4. Found: N, 9.2.

N,N'-Di-*ω*-carbomethoxyvaleryl-*N,N'*-dimethyl-*p*-phenylenediamine (II; R = CH₂OCO-(CH₂)₄) was prepared from the oxalate as above. It melted at 73–74°.

Anal. Calc'd for C₂₂H₂₂N₂O₄: C, 62.9; H, 7.6; N, 6.7.

Found: C, 63.1; H, 7.6; N, 6.6.

N,N'-Di-*p*-nitrobenzoyl-*N,N'*-dimethyl-*p*-phenylenediamine.¹ To a suspension of 15 g. of *N,N'*-dimethyl-*p*-phenylenediamine oxalate and 15.7 g. of sodium carbonate in 200 ml. of water, 29.5 g. of *p*-nitrobenzoyl chloride was added, with stirring, at room temperature during one-half hour, after which the whole was warmed at 50–60° for three hours. The cooled solution was filtered from the brownish solid, and the latter extracted with 350 ml. of boiling alcohol to remove *p*-nitrobenzoic acid. The crude residue (14.2 g.) was recrystallized from 200 ml. of glacial acetic acid; the acylated diamine separated as pale yellow needles; m.p. 256°.

In a similar manner there was prepared *N,N'*-di-*m*-nitrobenzenesulfonyl-*N,N'*-dimethyl-*p*-phenylenediamine; m.p. 215–217°, from dioxane or acetic acid, in 68% yield. It was also obtainable by using the free base instead of the oxalate, in which case the solution was allowed to stand at room temperature for two days instead of being heated. The *para*-nitro isomer melted above 300°. The di-*p*-nitrophenoxyacetyl (m.p. 233°) and 1-amino-2-naphthoxyacetyl derivatives (m.p. above 275°) were likewise prepared from the oxalate.

The 2-sulfo-4-nitrobenzoyl derivative was obtained as follows. The acid chloride of 2-sulfo-4-nitrobenzoic acid was first prepared from 43 g. of the potassium salt of the acid by means of 21 g. of thionyl chloride in 300 ml. of pyridine. To this solution was added 15 g. of the free base (prepared from the oxalate by making its aqueous suspension alkaline, shaking, extracting with ether, and removing the solvent) and the mixture stirred on the steam-bath for three hours. Upon cooling, 18 g. of the nitro compound separated.

The 1,4-bis-(2',4'-dinitrophenyl-*N*-methylamino)benzene was obtained by refluxing a mixture of 50 g. of the oxalate, 98.5 g. of 2,4-dinitrochlorobenzene, 76 g. of anhydrous sodium acetate, and 400 ml. of alcohol, with stirring, for five hours; the product that separated on cooling was removed and recrystallized from acetic acid, from which it separated in minute red-brown crystals, m.p. 238°.

All the nitroacyl compounds were reduced to the corresponding amines catalytically in alcohol in the presence of Raney nickel. The 2,4-dinitrophenyl derivative was reduced selectively, using sodium sulfide, but the location of the amino group was not determined. The melting points of the amines were as follows: *p*-aminobenzoyl, 255°, *m*-aminobenzene-sulfonyl, 218°; *p*-aminobenzenesulfonyl, 212–226°; *p*-aminophenoxyacetyl, 207°; 2(or 4)-amino-4(or 2)-nitrophenyl, 221°. Analytical figures for representative amines are collected in Table II.

Quaternary salts. The "double-ender" salt (XII; X = Cl) was formed very easily by merely warming a mixture of pyridine and *N,N'*-dichloroacetyl-*N,N'*-dimethyl-*p*-phenylenediamine until the solid was entirely dissolved. In a few minutes the salt began to separate, and soon the mixture was completely solid. It was triturated with acetone and the salt collected. The salt dissolved readily in methanol and water, but was insoluble in ether and acetone. It has no true melting point; if a specimen in a capillary tube is inserted in a bath, preheated to about 190°, it decomposes at about 195°.

¹ Dr. Walter A. Gregory assisted in the preparation of large quantities of certain of these intermediates.

Anal. Calc'd for $C_{22}H_{24}Cl_2N_4O_2$: Cl, 15.9. Found: Cl, 15.2.

The perchlorate (XII; $X = ClO_4$) separated on mixing aqueous solutions of the above chloride and sodium perchlorate. It required several crystallizations from water, using Norit, to get a colorless product. It decomposed above 220°.

bis-Azo dyes from the various diamines (Table I). These were all made in the same general way: (a) *Sulfonic acid group present.* The diamine (2.5 g.) was dissolved in hot hydrochloric acid (5 ml. of concentrated acid in 25 ml. of water), chilled to precipitate the salt in a finely-divided condition, and tetrazotized at 5° by sodium nitrite. After fifteen minutes, the solution was added, with stirring, to 3 g. of 1-naphthol-4-sulfonic acid in 35 ml. of water containing 2.8 g. of sodium hydroxide. The orange dye was salted out after one hour and purified by two re-saltings.

(b) *No sulfonic acid group.* The tetrazotization was performed in the same manner, and the solution added to a solution of an equivalent amount of the amine, dissolved in 5% hydrochloric acid. Coupling was brought about by adding a strong solution of sodium acetate; when coupling was complete, the dye was precipitated by the addition of aqueous sodium hydroxide.

(c) *Mixed disazo dye.* A representative dye was prepared by coupling the 4'-aminobenzoylethylamine (V) first with 2,4-diaminotoluene in acid solution, and then, after making strongly alkaline, with R salt. It dyes wool orange.

(d) *Trisazo dye.* The 4'-aminophenoxyacetylamine (IX) was tetrazotized and coupled first with *m*-aminooxanilic acid in weakly acid solution, and then with R salt in alkaline solution. A reddish dye separated; it was collected and dried. It was next diazotized and again coupled with R salt in alkaline solution; the dye slowly separated, was filtered off, and purified by dissolving and salting out with a saturated solution of sodium chloride. It dyes wool a maroon red.

(e) *Tetrazisazo dye.* The diamine (V) was tetrazotized as usual, and coupled in acid solution, pH 4.2, with 2-ethoxy-1-naphthylamine-6-sulfonic acid. The pH was raised first to 5.3 and then to 6.0, whereupon the dye precipitated. The dried dye was dispersed in very weak alkali, acidified and tetrazotized in the usual manner, and coupled with chromotropic acid in strongly alkaline solution. The brown dye was salted out with saturated salt solution. It dyes wool a dull reddish-brown, which becomes yellow-brown on top-chroming.

SUMMARY

sym.-Dimethyl-*p*-phenylenediamine has been acylated by a variety of acyl halides. The latter included long-chain aliphatic acyl, haloacyl, ω -carboalkoxyacyl, nitroarylcарoxy, nitroarylsulfonyl, and nitroaryloxyacyl chlorides, and 2,4-dinitrochlorobenzene.

The acyl derivatives were converted, by suitable manipulation, into azo dyes, and quaternary ammonium salts.

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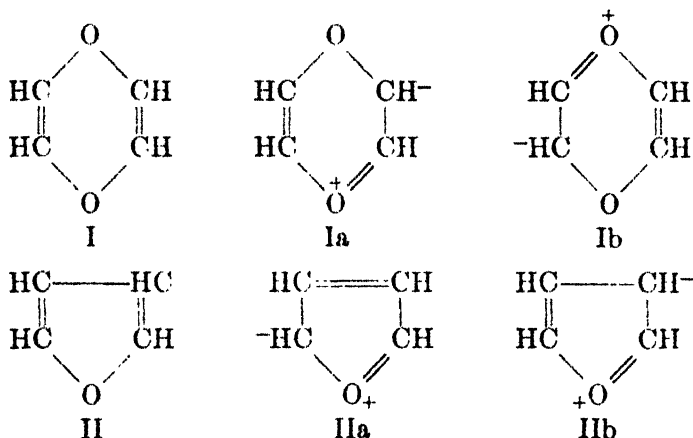
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ON THE AROMATIC CHARACTER OF DIOXADIENE

GERALD R. LAPPIN¹ AND R. K. SUMMERBELL*Received April 12, 1948*

The structural similarity of dioxadiene (I) to furan (II) has led to speculation concerning the possibility of this compound possessing aromatic character similar to that of furan. Aromatic character, usually attributed to resonance among several structures (as IIa and IIb) manifests itself physically in furan by alteration of the bond distances in normal structure II (1) and by contributing a resonance stability of 17.2 kcal. per mole to the molecule (2). Chemically this results in resistance of furan to addition reactions and increased ease of substitution in the furan nucleus. For example, the furan nucleus reacts with chlorine (3), bromine (3), nitric acid (4), and in the Friedel-Crafts acylation (5) to give substitution products. With metallic potassium furan gives 2-furyl potassium (6). All of these reactions have been used to define and evaluate aromatic character in heterocyclic compounds.



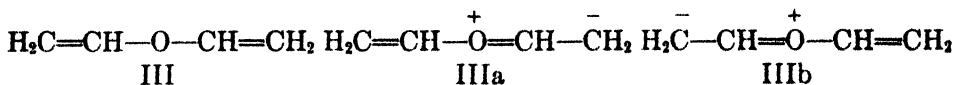
Dioxadiene could exhibit resonance similar to furan among such structures as Ia and Ib. This would be expected to result in physical and chemical manifestations similar to those in furan. Determination of the bond lengths in I has established that the deviations from the normal bond lengths are of the same magnitude as in the furan molecule (1). The ultraviolet absorption spectrum of I also indicates that structures such as Ia contribute to the state of the molecule (7). However, the only known chemical reactions of dioxadiene are those of an aliphatic unsaturated compound, for it reacts with hydrogen chloride, chlorine, and bromine to give addition products (8) and, on standing, polymerizes to an infusible substance (8). This investigation was undertaken in an attempt to discover whether dioxadiene exhibited any chemical manifestation

¹ Present address, Chemistry Department, Antioch College, Yellow Springs, Ohio.

of the aromaticity which physical measurements seem to indicate may be present in the molecule.

It has been found that dioxadiene does not react with any of the reagents commonly causing substitution in an aromatic compound. Nitric acid caused some oxidation of I to tarry material but no nitrodioxadiene could be isolated. When dioxadiene was heated with acid anhydrides or acid chlorides in the presence of such acylation catalysts as zinc chloride, ferric chloride, stannic chloride, and iodine no ketonic material could be detected and most of the dioxadiene could be recovered, the rest being accounted for as dioxadiene polymer. No reaction occurred between refluxing I and metallic potassium.

The conclusion must be drawn, therefore, that dioxadiene does not exhibit any aromatic character in its chemical reactions but behaves as a typical aliphatic unsaturated ether. Thus it should be compared to vinyl ether (III) which, though resonance is possible among forms such as IIIa and IIIb, has almost no resonance energy (2).



It undergoes no substitution reactions but readily adds bromine (9). When the possible resonance structures of furan, dioxadiene, and vinyl ether are compared it will be seen that the charge separation in some of the furan structures (as IIa) is only one bond length, while for the other two compounds all of the structures except the normal bond structure must have the much more unstable charge separation of two bond lengths. Thus the inherent instability of all but one of the possible resonance structures of dioxadiene would lead to an insignificant amount of resonance in this compound, resulting in turn in the manifestation of little or no aromatic character from the standpoint of chemical reactivity.

EXPERIMENTAL

Attempted nitration of I. A solution of 2.5 g. (0.03 mole) of dioxadiene in 15 ml. of acetic anhydride was cooled to 0° and to it was slowly added a solution of 20 g. of fuming nitric acid in 15 ml. of glacial acetic acid. The mixture, which became dark brown, was allowed to stand at room temperature for one hour and then poured over ice. The precipitated material was collected and found to consist of 2.2 g. (88%) of dioxadiene polymer identified by comparison with an authentic sample. No other material could be isolated except a small amount of tar.

Attempted acylation of I. A solution of 2.5 g. (0.03 mole) of I, 1.5 ml. of benzoyl chloride, and about 0.1 g. of anhydrous zinc chloride in 20 ml. of carbon disulfide was heated on the steam-bath for twenty-four hours. No hydrogen chloride was evolved. The solution was filtered, yielding 2.1 g. (84%) of dioxadiene polymer. The filtrate was treated with sodium carbonate solution to destroy the benzoyl chloride and the solvent was removed *in vacuo*. No precipitate was formed when the residue was treated with 2,4-dinitrophenylhydrazine.

This experiment was varied using acetic anhydride and acetyl chloride as acylating agents and using ferric chloride, stannic chloride, and iodine as catalysts. The use of other inert solvents and of excess of one reagent as solvent were also investigated. In every case only dioxadiene polymer could be isolated and no evidence of formation of ketonic products was found.

Attempted metallation of I. About 2 ml. of dioxadiene which had been freshly distilled from sodium was dissolved in 10 ml. of dry ether and 0.2 g. of clean potassium metal was added. The solution was refluxed for two days but no evidence of reaction was observed. Filtration of the solution gave 0.8 g. of dioxadiene polymer and distillation of the filtrate through a 10-cm. Vigreux column gave about 1 ml. of dioxadiene, representing a nearly quantitative recovery.

SUMMARY

The behavior of dioxadiene under conditions which yield various substitution products with furan was investigated. It was found that dioxadiene was not nitrated, acylated, or metallated under conditions for such reactions with furan. It was concluded, therefore, that chemically dioxadiene does not exhibit aromatic character but rather behaves as an unsaturated aliphatic ether comparable to vinyl ether.

EVANSTON, ILL.

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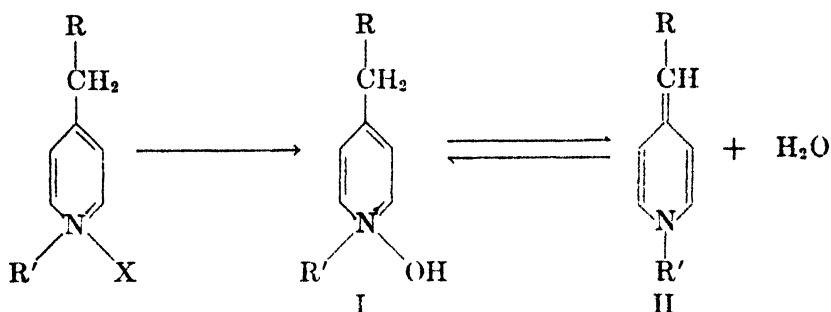
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4-BENZYL-2,6-DIMETHYLPYRIDINE, 1-BENZYLISOQUINOLINE,
9-BENZYLACRIDINE, AND CERTAIN RELATIVES

ERNEST H. HUNTRESS AND ELLIOTT N. SHAW ^{1,2}

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In his work on the quaternary hydroxides of six-membered nitrogenous heterocyclic bases formed from the corresponding quaternary halides by treatment with alkali, Decker regarded those having an alkyl group in α - or γ -relation to the ring nitrogen (I) as in equilibrium with what he termed an "anhydro base" (II). The hydroxides are generally colorless while the "anhydro bases" are yellow or orange (1, 2).



In the cases of α - and γ -(*p*-nitrobenzyl)pyridine (I, R = *p*-nitrophenyl) alkali treatment of the methiodide salt gave a deep blue color (3, 4, 5). This unusually strong color has been attributed either to increased activation of the methylene group or to *aci*-salt formation (3). No information is available as to the effect on the color of the anhydro base of other substituents in the benzene ring (R of II), or whether similar color phenomena accompany anhydro base formation in other heterocyclic series such as the isoquinolines or acridines when a *p*-nitrobenzyl group is the α - or γ -substituent. Some such cases have been examined in the present work.

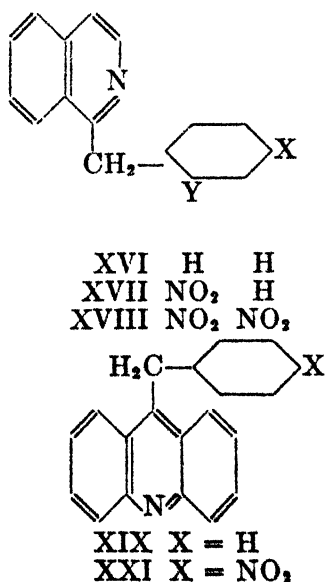
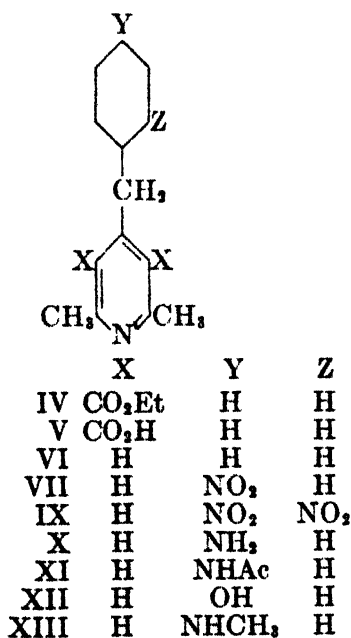
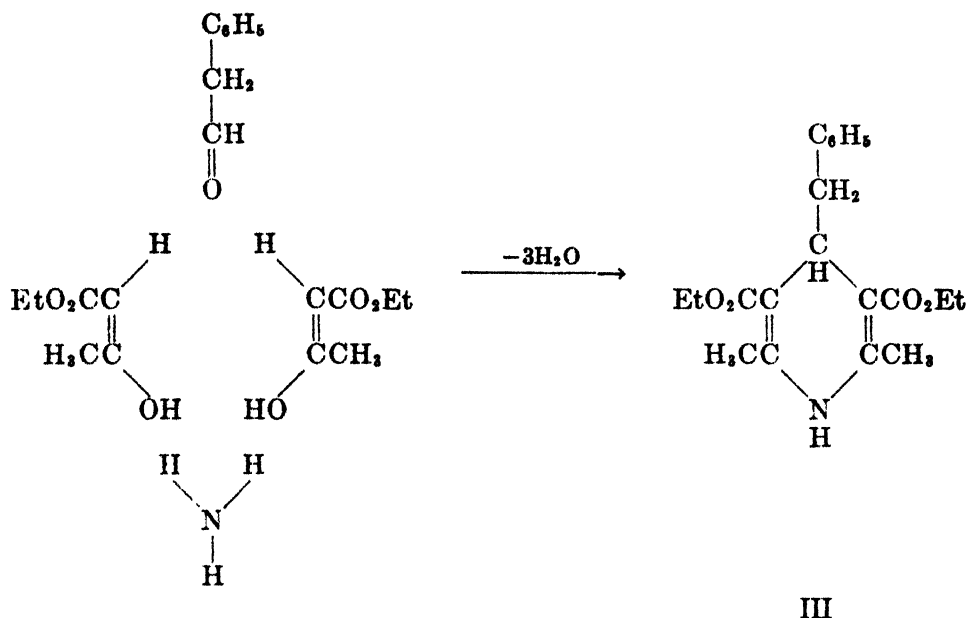
The hitherto unreported 4-benzyl-2,6-dimethylpyridine (VI) has been prepared and various substituents introduced into the *p*-position of its benzyl radical. Of these products, those which contain one or more nitro groups produce the most marked color change under circumstances leading to anhydro base formation (Table I). A marked color change also accompanies anhydro base formation in the case of 1-(4-nitrobenzyl)isoquinoline (XVII) but the result is blood-red (rather than blue). Similar treatment of 9-(4-nitrobenzyl)acridine (XXI), however, gives only the yellow color usually observed from unsubstituted bases.

Under the usual conditions characteristic of Hantzsch condensation phenylacetaldehyde condensed smoothly with two moles of ethyl acetoacetate and one

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² Present address: The Squibb Institute for Medical Research, New Brunswick, New Jersey.

of ammonia in alcohol solution to give in excellent yield diethyl 4-benzyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (III). This was readily dehydrogenated by heating with sulfur (6) to diethyl 4-benzyl-2,6-dimethylpyridine-3,5-dicarboxylate (IV). Saponification of this ester led to the salt of a dibasic acid (V) which on distillation



with lime in an inert atmosphere gave 4-benzyl-2,6-dimethylpyridine (VI). Mononitration of this base yielded 4-(4-nitrobenzyl)-2,6-dimethylpyridine (VII) in which the position of the nitro group was established by oxidation of VII [through the intermediate 4-(4-nitrobenzoyl)-2,6-dimethylpyridine VIII] to *p*-nitrobenzoic acid. Dinitration of VI or further nitration of VII yielded the same dinitro derivative, which is presumed to be 4-(2,4-dinitrobenzyl)-2,6-dimethylpyridine (IX). Reduction of VII with hydrogen and Adams' catalyst yielded 4-(4-aminobenzyl)-2,6-dimethylpyridine (X) which gave smoothly an acetyl derivative (XI), or after diazotization and appropriate hydrolysis the corresponding 4-(4-hydroxybenzyl)-2,6-dimethylpyridine (XII). On heating with methyl iodide, the primary amino group of (X) was partially methylated to 4-(4-methylaminobenzyl)-2,6-dimethylpyridine (XIII) which, however, was characterized only as its compound with one mole each of methyl iodide and hydrogen iodide (XIV).

TABLE I
METHIODIDES OF SUBSTITUTED 4-(R)-2,6-DIMETHYLPYRIDINES

R	M P UNCOR. OF METHIODIDE, °C.	COLOR	COLOR WITH ETHANOLIC KOH
Benzyl	150.5-152.0	Pink	Yellow
4-Nitrobenzyl	216-217	Yellow	Deep-blue
2,4-Dinitrobenzyl	210-211	Yellow	Deep-blue
4-Acetamino	193-194	White	Yellow
4-Methylamino	195-196	White	Yellow

The dehydrative cyclization of *N*-(β -phenylethyl)phenylacetamide with P_2O_5 (7) gave 1-benzyl-3,4-dihydroisoquinoline (XV), which upon dehydrogenation over palladium (7) served as a source of 1-benzylisoquinoline (XVI). Although both XV and XVI have previously been reported, our work led to the discovery that upon distillation of XV over potassium hydroxide cleavage occurs with resultant formation in excellent yield of both isoquinoline and toluene. Mononitration of 1-benzylisoquinoline (XVI) was effected by elimination of water from its nitrate salt and yielded 1-(4-nitrobenzyl)isoquinoline (XVII), in which the position of the nitro group was established by oxidation to *p*-nitrobenzoic acid. Dinitration of XVI led to a dinitro derivative (XVIII) in which the positions of the nitro groups have not been established but may, doubtless, be presumed to be *o*- and *p*- in the benzyl radical.

The conventional method (8) of heating together phenylacetic acid, diphenylamine, and zinc chloride provided 9-benzylacridine (XIX), whose nitrate (XX) readily dehydrated to 9-(4-nitrobenzyl)acridine (XXI), in whose structure the position of the nitro group was demonstrated by formation of *p*-nitrobenzaldehyde on chromic acid oxidation. Oxidation of XXI gave the corresponding ketone, to be regarded as 9-(4-nitrobenzoyl)acridine (XXII).

EXPERIMENTAL

2,6-Dimethylpyridine Series

Diethyl 4-benzyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (III). Phenylacetaldehyde (12 g. = 0.1 mole), ethyl acetoacetate (27 g. = 0.2 mole) in absolute ethanol containing 1.7 g. (0.1 mole) of dry ammonia were mixed in a pressure bottle which was sealed and stood at room temperature for 24 hours. Concentration of the alcoholic solution gave 23.5 g. (71% yield) of yellow solid which, after recrystallization from 75% methanol, gave colorless needles, m.p. 117–118° uncor.; recorded, 115° (9), 119° (6).

Diethyl 4-benzyl-2,6-dimethyl-3,5-dicarboxylate (IV). The dihydro compound (III, above) (18 g.) mixed with sublimed sulfur (1.68 g.) was heated in a test tube at 200°, the molten contents being efficiently stirred to facilitate evolution of hydrogen sulfide. Reaction was generally complete in 30 minutes. The oily product from several runs in which a total of 71 g. of dihydro compound had been used gave, upon fractionation, 57 g. (80% yield) of pale yellow oil, b.p. 199–204° at 10 mm. On standing, or when seeded, the oil solidified, and recrystallization from ethyl acetate gave transparent plates, m.p. 47.0–48.5°; recorded, 46° (6).

4-Benzyl-2,6-dimethylpyridine-3,5-dicarboxylic acid (V). The diethyl ester (IV) (40 g.) was saponified with potassium hydroxide (60 g.) in absolute ethanol (200 ml.). The solution was refluxed for 5 hours, during which the yellow potassium salt gradually separated. After filtration of this solid, additional material was obtained by concentration of the filtrate. Subsequent crops of salt became increasingly hygroscopic due to contamination with free alkali, making exact determination of yield impracticable, but the hydrolysis appears to be quantitative. This economical and convenient method of isolation is preferred to that of precipitation by addition of large volumes of ether (10).

The salt so obtained was dissolved in water and made neutral to litmus. Upon addition of two equivalents of 12 *N* hydrochloric acid, a white precipitate formed and redissolved in the hot solution. After decolorizing with charcoal and cooling, the acid was obtained as a white solid, m.p. 257–258° uncor., with evolution of carbon dioxide.

Anal. Calc'd for $C_{18}H_{15}NO_4$: N, 4.91; Neut. Equiv., 142.5.

Found: N, 4.98, 5.16, Neut. Equiv., 138.

4-Benzyl-2,6-dimethylpyridine (4-benzyl-2,6-lutidine) (VI). The acid (V) was decarboxylated by heating its dipotassium salt (10 g.) with calcium hydroxide (20 g.). A combustion tube of Corning 172 Pyrex tubing (19 mm. inside x 25 mm. outside diameter) supported horizontally in a V-shaped trough and heated with three burners served very satisfactorily after ordinary Pyrex tubing had been found insufficiently heat-resistant. A passage was left along the top of the charge to permit free flow of gases. After flushing out the charged tube with nitrogen, full heat was applied, the top of the tube being covered with asbestos board. The distillate was condensed in a flask cooled by flowing water. Accumulated distillates from potassium salt obtained from 48 g. of phenylacetaldehyde were combined, dried in ether over potassium hydroxide and fractionated, giving 24 g. of 4-benzyl-2,6-lutidine, b.p. 167–169° at 17 mm., n_D^{25} 1.5686 as a colorless oil with pale yellow-blue fluorescence. This result represents a 30% over-all yield from phenylacetaldehyde.

4-Benzyl-2,6-lutidine picrate. Orange rods, m.p. 142–143° uncor.

Anal. Calc'd for $C_{20}H_{15}N_4O_7$ (i.e., $C_{14}H_{11}N \cdot C_6H_5N_3O_7$): N, 13.15.

Found: N, 12.9, 13.2.

4-Benzyl-2,6-lutidine methiodide. Lustrous pink or yellow flakes from alcohol-ether, m.p. 150.5–152.0° uncor.

Anal. Calc'd for $C_{15}H_{13}IN$ (i.e., $C_{14}H_{11}N \cdot CH_3I$): N, 4.13; I, 37.4.

Found: N, 4.50; I, 37.9.

4-(4-Nitrobenzyl)-2,6-dimethylpyridine (VII). 4-Benzyl-2,6-lutidine (VI) (10 g.) was shaken in a separatory funnel with 30 ml. of 2 *N* nitric acid saturated with sodium nitrate. The lower aqueous layer was drawn off and the upper layer (presumably the base nitrate)

was shaken with ether (20 ml.), then added dropwise with stirring to concentrated sulfuric acid (35 ml.) cooled in an ice-bath. The sulfuric acid solution was brought to 50° for 5 minutes, poured onto ice, made neutral with sodium carbonate, and extracted with benzene. Decolorization and evaporation of the solvent gave a crude product, m.p. 132–135°; recrystallization from alcohol with addition of water gave (40% yield) white needles of m.p. 135.5–136.5° uncor.

Anal. Calc'd for $C_{14}H_{14}N_2O_2$: N, 11.6. Found: N, 11.5, 11.6.

4-(4-Nitrobenzyl)-2,6-dimethylpyridine methiodide. Yellow crystals from ethanol, m.p. 216–217° uncor.

Anal. Calc'd for $C_{15}H_{17}IN_2O_2$: N, 7.28; I, 33.1.

Found: N, 7.40; I, 33.4.

4-(4-Nitrobenzoyl)-2,6-dimethylpyridine (VIII). A small sample of the above nitro compound (VII) (0.55 g.) suspended in boiling water (40 ml.) was slowly treated with 5% aqueous potassium permanganate, each addition of oxidant being made only when its predecessor had been almost consumed. The total time involved was 22 hours, after which the excess permanganate was decolorized with ethanol and the hot solution filtered. From the aqueous filtrate on cooling, and from benzene extraction of the manganese dioxide cake, there was obtained 0.2 g. of the desired ketone.

Anal. Calc'd for $C_{14}H_{12}N_2O_3$: N, 10.95. Found: N, 10.8, 10.9.

From the aqueous filtrate on concentration and acidification there was also obtained 0.11 g. of *p*-nitrobenzoic acid, m.p. 235–236°, alone or mixed with an authentic sample.

4-(4-Aminobenzyl)-2,6-dimethylpyridine (X). A solution of 4-(4-nitrobenzyl)-2,6-lutidine (VII) (3.43 g.) in 95% ethanol (70 ml.) together with platinum oxide (47 mg.) was shaken with hydrogen at atmospheric pressure and room temperature. After the theoretical amount of hydrogen for reduction of the nitro group had been taken up, rate of absorption of gas sharply decreased. After filtering off the catalyst and evaporating the solvent, there remained 2.8 g. (93% yield) of product recrystallization of which from 40% methanol gave colorless needles, m.p. 132–133° uncor.

Anal. Calc'd for $C_{14}H_{16}N_2$: N, 13.2. Found: N, 13.0, 13.4.

4-(4-Acetaminobenzyl)-2,6-dimethylpyridine (XI). This was obtained from the above base (X) with acetic anhydride; m.p. 145–146° uncor.

Anal. Calc'd for $C_{16}H_{18}N_2O$: N, 11.0. Found: N, 10.9, 11.0.

4-(4-Acetaminobenzyl)-2,6-dimethylpyridine methiodide. White crystals from ethanol, m.p. 193–194° uncor.

Anal. Calc'd for $C_{17}H_{21}IN_2O$: N, 7.07. Found: N, 7.78.

4-(4-Methylamino)-2,6-dimethylpyridine methiodide hydriodide (XIV). 4-(4-Aminobenzyl)-2,6-dimethylpyridine (0.5 g.) with methyl iodide (4 ml.) in a sealed tube at 90° for 6 hours effected monomethylation of the amino group, subsequently quaternizing on one nitrogen and forming the hydriodide salt on the other. The product (0.3 g.) formed white crystals, m.p. 195–196° uncor.

Anal. Calc'd for $C_{15}H_{22}I_2N_2$: C, 38.7; H, 4.44.

Found: C, 38.4, 38.7; H, 4.55, 4.72.

4-(4-Hydroxybenzyl)-2,6-dimethylpyridine (XII). Diazotization of 4-(4-aminobenzyl)-2,6-lutidine (X) (0.7 g.) was carried out in 16% sulfuric acid (40 ml.) by addition at 0° of sodium nitrite (0.23 g.) in water (5 ml.). More water (20 ml.) was added and the solution heated for 2 hours at 100°. The solution was made alkaline with sodium carbonate and extracted with ether. Evaporation of the ether gave a solid which, after purification from alcohol by addition of water, gave 0.4 g. (57% yield) of product which was finally raised to m.p. 163–164° uncor.

Anal. Calc'd for $C_{14}H_{14}NO$: N, 6.58. Found: N, 6.66, 6.66.

4-(2,4-Dinitrobenzyl)-2,6-dimethylpyridine (IX). 4-Benzyl-2,6-lutidine (VI) (3 g.) dissolved in concentrated sulfuric acid (17 ml.) was treated dropwise with fuming nitric acid (1.5 ml., *d*, 1.5) with cooling. After two hours at room temperature the solution was poured onto ice, made alkaline with sodium carbonate and extracted with benzene. Concentration

of the solvent gave 2.2 g. (50% yield) of product which on recrystallization from benzene gave white needles, m.p. 139.5° uncor.

Anal. Calc'd for $C_{14}H_{13}N_2O_4$: N, 14.6. Found: N, 14.1, 14.2.

The melting point of this compound was not depressed when mixed with the product of treatment of 4-(4-nitrobenzyl)-2,6-lutidine (0.25 g.) in concentrated sulfuric acid (5 ml.) with concentrated nitric acid (0.4 ml., *d*, 1.42) at 70° for 1 hour, followed by usual isolation.

4-(2,4-Dinitrobenzyl)-2,6-dimethylpyridine methiodide. Yellow crystals from ethanol, m.p. 210–211° uncor.

Anal. Calc'd for $C_{15}H_{14}IN_2O_4$: N, 9.79. Found: N, 10.2.

Isoquinoline Derivatives

1-Benzyl-3,4-dihydroisoquinoline (XV). This base was obtained from N-(2-phenylethyl)phenylacetamide (11), m.p. 92–93° uncor. by dehydrative cyclization essentially according to Späth (7). The amide (20 g.) dissolved in boiling tetralin (400 ml.) was treated with phosphorus pentoxide (40 g.); after 15 minutes a second equal portion (40 g.) of phosphorus pentoxide was added and boiling continued for 15 more minutes. The tetralin was decanted from the brown residue, to which water was then very carefully added. All of the solid was finally dissolved with a total of 300 ml. of water. A second layer of tetralin was then removed and the phosphoric acid layer extracted with ether to remove the last traces. By neutralizing the acid solution with solid sodium hydroxide the dihydro base was liberated as a brown oil. After drying in ether over potassium hydroxide fractionation gave the base (15.5 g., 84% yield), b.p. 195–198° at 2 mm., n_D^{20} 1.6167. The corresponding picrate showed m.p. 173.5–175°; recorded, 182° uncor. (11), 173–175° (7), 174–175° (12).

When the ether extract from a ring closure such as described above was distilled from potassium hydroxide pellets, an unexpected cleavage occurred with formation of isoquinoline and toluene in good yield, as shown in the following example. Half of the ether solution from a typical cyclization on distillation without potassium hydroxide gave 8.9 g. of 3,4-dihydroisoquinoline. The other half was concentrated over potassium hydroxide pellets in a Claisen flask from which (after ether removal) raising of bath temperature to 200° caused distillation over about an hour of a colorless liquid. Refractionation of this material gave 2.5 g. of toluene, b.p. 107–110° confirmed by neutral permanganate oxidation to benzoic acid. Reduction of pressure to 5 mm. then yielded a second distillate (3.8 g., b.p. 95° at 5 mm.) which was shown to be isoquinoline by preparation of the corresponding methiodide and picrate and direct comparison with authentic samples. The picrate was also confirmed by satisfactory analyses for nitrogen and for neutralization equivalent.

1-Benzylisoquinoline (XVI). Samples of 1-benzyl-3,4-dihydroisoquinoline (XV) were dehydrogenated over palladium black at 190° as previously reported (7), yielding 1-benzylisoquinoline, b.p. 160–162° at 2 mm.; corresponding picrate, m.p. 179–181° uncor [recorded, 184–185° cor. (13), 184° cor. (14), 182° (7, 12), 182–184° (15), 176° (16)].

This base (1 g.) with methyl iodide (10 ml.) in a sealed tube at 100° for 10 minutes gave benzylisoquinoline methiodide (1.8 g.) which recrystallized from alcohol as pale yellow crystals, m.p. 229–231° uncor.; recorded 248° cor. (14).

Anal. Calc'd for $C_{17}H_{18}IN$: N, 3.88. Found: N, 4.02, 4.07.

1-(4-Nitrobenzyl)isoquinoline (XVII). 1-Benzylisoquinoline (XVI) (3 g.) was mononitrated by essentially the same procedure used for 4-benzyl-2,6-lutidine (VI). The orange oil comprising the crude product distilled at 218–220° at 1.5 mm. and gave 1.85 g. = 51% yield. Subsequent solidification slowly occurred, after which recrystallization from dilute ethanol yielded white needles, m.p. 85–86°.

Anal. Calc'd for $C_{18}H_{17}N_2O_2$: N, 10.6. Found: N, 10.7, 11.2.

After conversion of this compound to its methiodide and oxidation of a boiling aqueous solution of the latter with potassium permanganate, there was isolated *p*-nitrobenzoic acid, m.p. 233–235°, which did not depress the melting point of an authentic sample.

1-(2,4-Dinitrobenzyl)isoquinoline (XVIII). 1-Benzylisoquinoline (XVI) (1.5 g.) was dinitrated by solution in concentrated sulfuric acid (12 ml.) and treatment at room tempera-

ture with concentrated nitric acid (1.5 ml., *d*, 1.42). After standing for one hour, pouring onto ice and working up there resulted 0.26 g. (12% yield) of crude product, recrystallization of which from 50% ethanol gave yellow flakes, m.p. 160–162° uncor.

Anal. Calc'd for $C_{14}H_{11}N_3O_4$: N, 13.6. Found: N, 13.4, 13.8.

Acridine Derivatives

9-Benzylacridine (XIX). This material was prepared from phenylacetic acid, diphenylamine, and fused zinc chloride by heating at 190–200° for 24 hours as described in the literature (8); yield 21%; from benzene it separated as yellow crystals, m.p. 174–175° uncor.; recorded 173° (8, 17).

9-Benzylacridinium nitrate (XX). 9-Benzylacridine, on boiling with 3 *N* nitric acid for 10 minutes did not dissolve, and the only apparent change was an increase in the hardness of the yellow solid. Recrystallization of the material by solution in glacial acetic acid and reprecipitation with dry ether gave yellow needles of 9-benzylacridine nitrate, m.p. 167–168° uncor.

Anal. Calc'd for $C_{20}H_{15}N_2O_2$: N, 8.44. Found: N, 8.38, 8.40.

9-(4-Nitrobenzyl)acridine (XXI). 9-Benzylacridinium nitrate (XX) (1.68 g.) was dissolved in concentrated sulfuric acid (20 ml.). The solution was brought to 50°, poured over ice, and made alkaline with concentrated ammonium hydroxide. The resultant pink solid was separated, dissolved in boiling absolute ethanol (110 ml.), decolorized with carbon, and reprecipitated by addition of water (40 ml.) as lustrous golden flakes, 1.4 g. = 75% yield, m.p. 195–198° uncor.

Anal. Calc'd for $C_{20}H_{14}N_2O_2$: N, 8.92. Found: N, 9.16, 9.24.

9-(4-Nitrobenzyl)acridine methiodide. 9-(4-Nitrobenzyl)acridine (0.2 g.) with methyl iodide (10 ml.) in a sealed tube heated for 20 minutes gave deep red rods of quaternary salt (0.12 g.) which did not melt up to 250°. The yield was not increased by longer heating. The salt was sparingly soluble in water but gave an immediate precipitate with silver nitrate solution.

Anal. Calc'd for $C_{21}H_{17}IN_2O_2$. I, 27.9. Found. I, 28.0.

9-(4-Nitrobenzyl)acridine (XXII) 9-(4-Nitrobenzyl)acridine (0.5 g.) in glacial acetic acid (10 ml.) containing sodium dichromate (0.4 g.) was refluxed for 2 hours. Water (40 ml.) was then added, precipitating a gummy solid which on recrystallization from alcohol gave yellow crystals (0.01 g.), m.p. 226–228° uncor.

Anal. Calc'd for $C_{20}H_{12}N_2O_4$: N, 8.53. Found: N, 8.61.

Unlike the isomeric nitroacridones (18) this material gave no color with alcoholic alkali.

CAMBRIDGE 39, MASS.

SUMMARY

1. A hitherto unreported base, 4-benzyl-2,6-dimethylpyridine, has been synthesized and characterized.
2. The color reactions produced by alcoholic alkali upon the quaternary salts of 4-(4-nitrobenzyl)-2,6-dimethylpyridine, 1-(4-nitrobenzyl)isoquinoline, and 9-(4-nitrobenzyl)acridine have been compared.
3. Including those above 20 new compounds have been characterized.
4. 1-Benzyl-3,4-dihydroisoquinoline, when distilled with alkali, has been found to split into good yields of toluene and isoquinoline.

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CRYSTALLINE PHENYLISOCYANATE DERIVATIVES FROM BENZYLPENICILLOIC ACID AND α -METHYL BENZYLPENICILLOATE

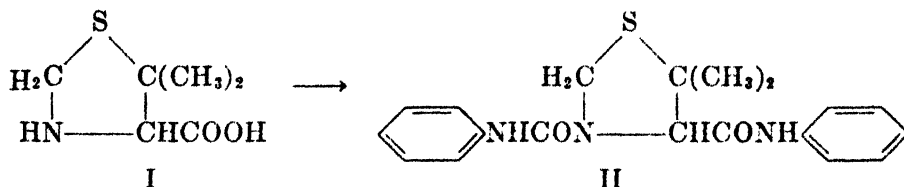
SELBY B. DAVIS, STUART D. WILLSON, AND R. BRUCE VAN ORDER¹

Received April 14, 1948

Early in the course of an investigation of the structure of penicillin² it was observed that treatment of the latter with cold, aqueous alkali resulted in the production of a new substance, benzylpenicilloic acid. The release of 1 mole of acid during the course of the reaction, the difference between the empirical formula of the product, $C_{16}H_{20}N_2O_5S$, and that of benzylpenicillin, $C_{16}H_{18}N_2O_4S$, and the differences between the infrared spectra of the two, indicated that the treatment with alkali had effected hydrolysis of an inner anhydride. The isolated product, however, proved refractory to crystallization, and was of indefinite melting point. Furthermore, the specific rotation of repeated preparations differed greatly, ranging from 73° to 120° (sodium bicarbonate solution).

A number of attempts were made to prepare a crystalline derivative of definite physical properties. The sodium, potassium, ammonium, and S-(*p*-bromobenzyl)thiuronium salts could not be obtained in crystalline form. Attempted acylation with ketene in acetone solution, and with benzoyl chloride in alkali or in pyridine, led to intractable oils. Crystallization of the oily picrate was not effected. The initial, partially crystalline precipitates produced by treatment with ammonium Reineckate and with ammonium rhodanilate were of inconstant composition and decomposed on attempted recrystallization.

It was then observed that treatment of the model compound, 5,5-dimethylthiazolidine-4-carboxylic acid (I), with phenylisocyanate led to a crystalline dicarbanilinodimethylthiazolidine (II), m.p. $217-217.5^\circ$, the structure of which was evident from its properties and the known reactivity of carboxyl (2) and amino groups with phenylisocyanate.

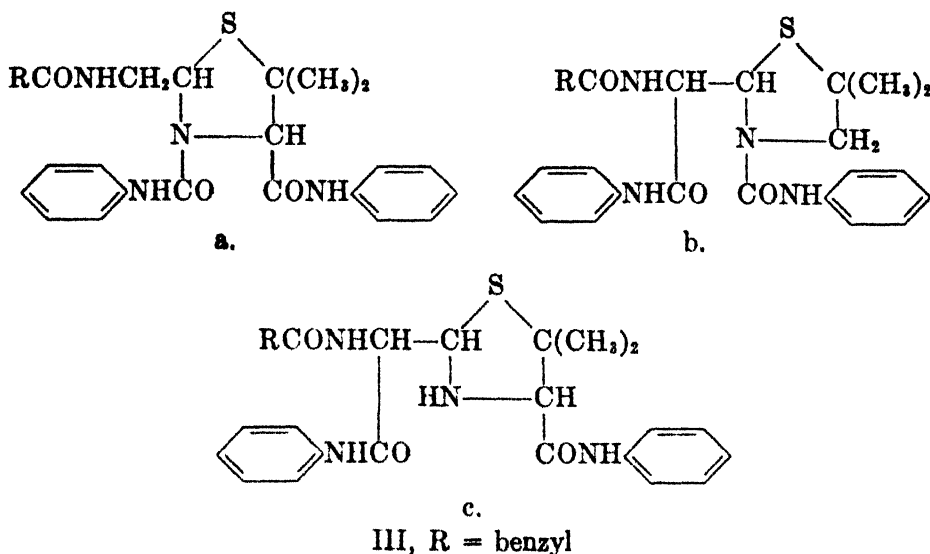


When benzylpenicilloic acid was treated with phenylisocyanate a crystalline derivative was likewise obtained. The empirical formula, $C_{28}H_{30}N_4O_5S$, of the product, m.p. $221-222^\circ$, $(\alpha)_D^{22} -100^\circ$, indicated that two carboxyl groups had

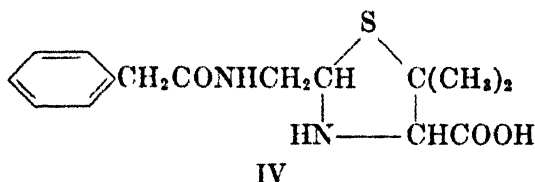
¹ Present address: Calco Chemical Division, American Cyanamid Company, 338 Wilson Avenue, Newark, New Jersey.

² Our crystalline isolate, upon which this work was begun (1944) has proved identical with what is now known as benzylpenicillin (1). The latter nomenclature has been; used throughout the present report.

been lost and two carbanilino groups had been introduced during the course of the reaction. The infrared spectrum (Fig. 1) resembled that of the derivative (II) of the model compound, but showed significant differences in the frequencies of several major absorption bands. Of the tentative structures (IIIa, b, and c), deducible from the above data and the previously characterized breakdown products of benzylpenicilloic acid (3, 4), structure (IIIa) appeared most probable.



Synthesis of optically inactive 5,5-dimethyl-2-phenacetylaminomethylthiazolidine-4-carboxylic acid (IV) was



accomplished by condensation of phenacetylaldehyde with racemic β,β -dimethylcysteine. The amorphous product yielded a crystalline derivative, $C_{23}H_{30}N_4O_3S$, m.p. 207–208°, on treatment with phenylisocyanate. Comparison of the infrared spectrum of this substance with that of the phenylisocyanate derivative obtained from benzylpenicilloic acid showed the two to agree at all points (Fig. 1), establishing structure (IIIa) for the derivative from benzylpenicilloic acid.

Like the product of alkaline hydrolysis, the product of methanolysis of benzylpenicillin, α -methyl benzylpenicilloate, was ill-characterized because of its lack of crystallinity, its indefinite melting point, and the differing specific rotation of successive preparations. Application of the phenylisocyanate reaction to this substance yielded a crystalline derivative, $C_{30}H_{32}N_4O_5S$, m.p. 170–172°, $(\alpha)_D^{24} +46^\circ$. The properties of this substance, and the previous characterization of

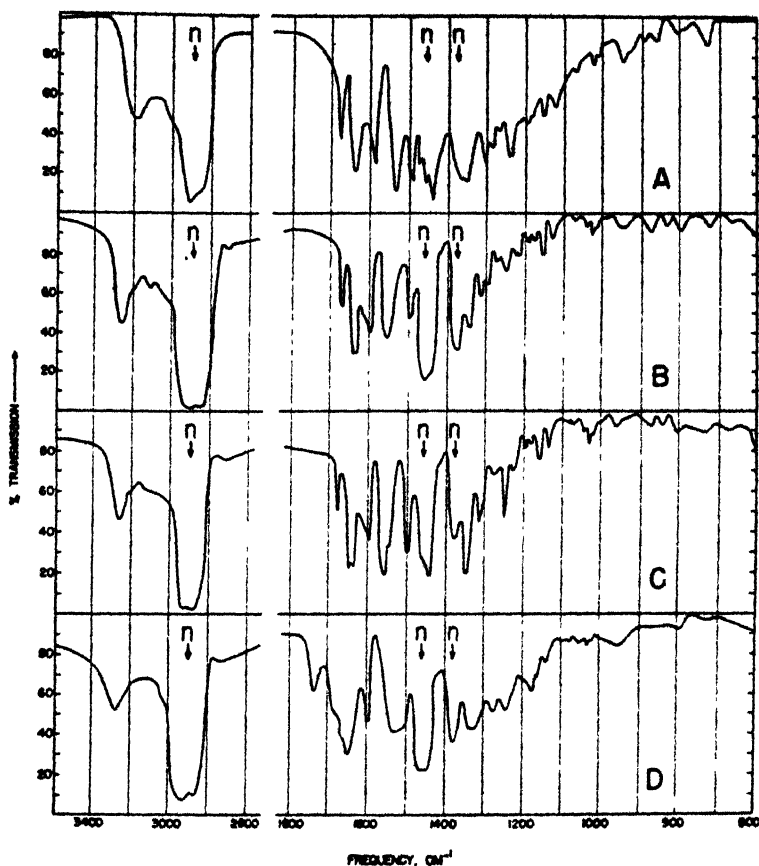


FIG. 1. INFRARED ABSORPTION SPECTRA

n. Absorption band due to Nujol.

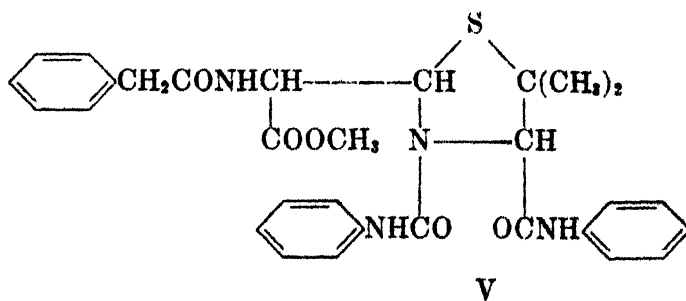
A. 3,4-Dicarbanilino-5,5-dimethylthiazolidine (II).

B. Phenylisocyanate derivative from benzylpenicilloic acid (IIIa).

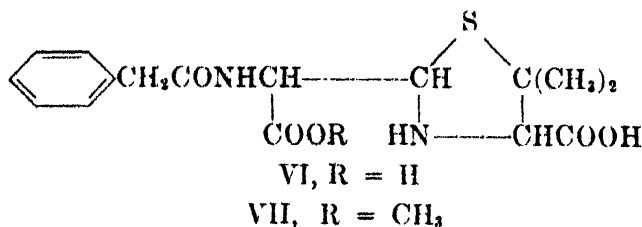
C. 3,4-Dicarbanilino-5,5-dimethyl-2-phenacetylaminothiazolidine (IIIa).

D. Phenylisocyanate derivative from α -methyl benzylpenicilloate (V)

the breakdown products of methyl benzylpenicilloate (3, 4) served to establish its structure as (V).



The structures of benzylpenicilloic acid (VI) and α -methyl benzylpenicilloate (VII), deduced from the above data, agree with those published (4).



ACKNOWLEDGMENT

We are grateful to Dr. R. O. Roblin, Jr. of these Laboratories for encouragement and suggestions, and to Misses E. P. Anderson, R. A. Rhodes, and N. E. Shakespeare for aid in the experimental work.

EXPERIMENTAL³

3,4-Dicarbanilino-5,5-dimethylthiazolidine (II). A mixture of 50 mg. of 5,5-dimethylthiazolidine-4-carboxylic acid,⁴ with 163 mg. of phenylisocyanate was warmed gently until the evolution of gas had virtually ceased. The mixture was then heated for one and one-half hours at 100°. The cooled reaction mixture was triturated with six 0.3-cc. portions of ether, and the solid residue was dried under vacuum. Crystallization of the crude product, 93 mg., m.p. 196–199°, from a minimum quantity of absolute ethanol, yielded 44 mg. (40%) of essentially pure 3,4-dicarbanilino-5,5-dimethylthiazolidine as colorless, columnar crystals, m.p. 215–216.5°. The substance was found to be insoluble in water, 5% sodium bicarbonate, 10% sodium hydroxide, and 10% hydrochloric acid; slightly soluble in petroleum ether, benzene, carbon tetrachloride, ether, and chloroform; moderately soluble in acetone and ethanol; and readily soluble in pyridine. Recrystallization from absolute ethanol prior to analysis raised the m.p. to 217–217.5°.

^{3a} Certain of the compounds described in this section have been independently prepared by various groups collaborating with the Committee on Medical Research, O.S.R.D., Washington: 5,5-dimethylthiazolidine-4-carboxylic acid, Cornell University Medical College, *D.* 2, 3, February 3, 1944; benzylpenicilloic acid, Merck & Company, *M.* 33, 2, June 30, 1944; phenacetylaminomethylthiazolidine-4-carboxylic acid, The Upjohn Company, *U.* 4, 12, March 15, 1944; 5,5-dimethyl-2-phenacetylaminomethylthiazolidine-4-carboxylic acid, The Upjohn Company, *U.* 4, 14, March 15, 1944; α -methyl benzylpenicilloate, Abbott Laboratories, *A.* 3, 3, February 14, 1944. After completion of the present work the foregoing reports were made available to us through the courtesy of Professor Hans T. Clarke, College of Physicians and Surgeons, Columbia University.

^{3b} All melting points were determined on the Fisher-Johns block.

⁴ We are indebted to Dr. E. W. Cook of the Organic Research Division, these Laboratories for a sample of this substance. 5,5-Dimethylthiazolidine-4-carboxylic acid, m.p. 212–213° (dec.), was prepared from β , β -dimethyleysteine and formaldehyde following the thiazolidine-4-carboxylic acid synthesis of Ratner and Clarke (5). β , β -Dimethyleysteine, m.p. 205–206° (dec.), was synthesized by nitration of ethyl dimethylacrylate with nitric acid, addition of benzylmercaptan to the α -nitroester, reduction of the nitro group with tin and hydrochloric acid, acid hydrolysis of the ester, and removal of the benzyl group with sodium in liquid ammonia. An alternative synthesis has since been published (6).

*Anal.*⁵ Calc'd for $C_{19}H_{21}N_3O_2S$: C, 64.20; H, 5.96; N, 11.82; S, 9.02. Mol. wt., 355.4.

Found: C, 64.62; H, 6.28; N, 11.65; S, 8.66. Mol. wt. (Rast), 356.

Benzylpenicilloic acid (VI). A solution of 199 mg. of crystalline sodium benzylpenicillin⁶ in 6 cc. of distilled water at 25° was maintained at pH 11.4 by the intermittent addition of 0.5002 *N* sodium hydroxide for two hours. By this time the release of acid had become negligible; total alkali required at pH 11.4, 0.601 milliequivalents, corresponding to a release of 1.08 moles of acid per mole of penicillin. After standing for a further one-half hour at pH 11.4 the solution was acidified to pH 2 with 0.5 *N* sulfuric acid and extracted with five 2-cc. portions of butanol. The solvent was removed from the combined extract under vacuum at room temperature. The residue, a colorless glass, was taken up in 5 cc. of acetone, the solution was centrifuged to remove a small portion of insoluble material, and the supernate was evaporated in a stream of nitrogen. Trituration of the residue with three 1.5-cc. portions of ether, followed by drying at room temperature under vacuum, reduced the residue to a white powder consisting of microscopic, nonbirefringent,⁷ glassy platelets of benzylpenicilloic acid. Yield, 167 mg. (85%), m.p. ca. 112°, (α)_D²⁰ +120° (5% sodium bicarbonate, c, 0.453), (α)_D²⁰ +83° (abs. ethanol, c, 0.461). Assay,⁸ <0.02 units/mg. The substance was slightly soluble in petroleum ether, benzene, and carbon tetrachloride; moderately soluble in ether, chloroform, and water; readily soluble in acetone, ethanol, pyridine, 5% sodium bicarbonate, 10% sodium hydroxide, and 10% hydrochloric acid.

Anal. Calc'd for $C_{18}H_{20}N_2O_2S$: C, 54.54; H, 5.72; N, 7.95; S, 9.10. Active H (4 atoms per mole), 1.12. Equiv. wt., 176.2.

Found: C, 54.61, 54.41; H, 6.00, 5.99; N, 7.78, 7.79; S, 9.34. Active H (Zerewitinoff), 1.07, 1.09. Equiv. wt., 163, 158; pK_{a1} = 2.4, pK_{a2} = 5.2.

Phenylisocyanate derivative from benzylpenicilloic acid (IIIa). A mixture of 196 mg. of benzylpenicilloic acid and 640 mg. of phenylisocyanate was warmed until gas evolution had ceased and was then heated at 100° for one and one-half hours. The reaction mixture was triturated with eight 1.5-cc. portions of ether, and the residue was dried under vacuum, yielding 146 mg. of yellow, crystalline powder, m.p. 184–189° (previous softening). Continuous extraction with ether for seven hours removed most of the *sym*-diphenylurea and low-melting by-products, leaving 110 mg. of colorless crystals, m.p. 191–196°. Final purity was reached only after four crystallizations from absolute ethanol, which yielded 22 mg. (8%) of rosettes of fine, colorless needles of the phenylisocyanate derivative, m.p. 221–222°, (α)_D²⁰ –100° (pyridine, c, 0.488). The solubility in various solvents was similar to that of 3,4-dicarbanilino-5,5-dimethylthiazolidine.

*Anal.*⁹ Calc'd for $C_{22}H_{20}N_4O_2S$: C, 66.91; H, 6.02; N, 11.15; S, 6.38.

Found: C, 66.76, 66.67; H, 6.31, 6.39; N, 11.01; S, 6.24.

Phenacetyl aminoacetal. Aminoacetal was prepared according to Organic Syntheses (8). A 15.5-g. portion of commercial phenacetyl chloride was added to an ice-cold solution of 13.3 g. of aminoacetal and 10.6 g. of anhydrous sodium carbonate in 100 ml. of water. After standing at room temperature for twenty-four hours with intermittent shaking, the mixture was extracted three times with 15-cc. portions of ether. The combined extract was twice

⁵ Analyses were performed by the Microanalytical Laboratory, Technical Service Division, these Laboratories, under the direction of Dr. J. A. Kuck, except as otherwise noted.

⁶ These experiments were begun on a crystalline sample (1650 units/mg.) prepared by the authors (3) from crude sodium salt (150 units/mg.) furnished by the Lederle Laboratories Division, American Cyanamid Company. For later samples of crystalline sodium benzylpenicillin we are indebted to Mr. E. F. Williams of the Physics Division, these Laboratories.

⁷ We are indebted to Dr. A. F. Kirkpatrick of the Physics Division, these Laboratories, for all microscopic examinations reported.

⁸ We are grateful to Misses Nydia Ananenko and Marion Cook for the assays, which were performed by the paper-disc method of Vincent and Vincent (7).

⁹ Huffman Microanalytical Laboratories, Denver, Colorado.

washed with 100-cc. portions of 0.05 *N* sulfuric acid, dried over sodium sulfate, and evaporated leaving 12.9 g. of orange oil. Molecular distillation of the crude product at 8×10^{-4} mm., bath temperature 135–140°, yielded 9.6 g. (38%) of essentially pure phenacetylaminomethylthiazolidine-4-carboxylic acid, which crystallized on cooling to room temperature. A recrystallized sample, m.p. 35–37°, was prepared by adding several volumes of petroleum ether to a concentrated ether solution of the substance.

Anal. Calc'd for $C_{14}H_{21}NO_4$: N, 5.57. Found: N, 5.63, 5.74.

5,5-Dimethyl-2-phenacetylaminomethylthiazolidine-4-carboxylic acid (IV). A solution of 2.5 g. of phenacetylaminomethylthiazolidine-4-carboxylic acid in 60 cc. of 95% ethanol was cooled in an ice-bath during the addition of 150 cc. of *N* sulfuric acid. The mixture was allowed to stand at room temperature for two and one-half hours and finally heated to 90° to complete hydrolysis of the acetal. After cooling to room temperature, 12.6 g. of sodium bicarbonate was added to bring the solution to neutrality and 1.5 g. of racemic β,β -dimethylcysteine,⁴ was stirred in. After the addition of further sodium bicarbonate to pH 8 the mixture was allowed to stand at room temperature for twenty-four hours with occasional shaking. The solution was then evaporated to a volume of ca. 100 cc. at a maximum temperature of 50°, and extracted with three 20-cc. portions of butanol to remove unreacted aldehyde. After acidification to pH 2 with 6 *N* sulfuric acid, the solution was again extracted three times with 20-cc. portions of butanol. The extract was evaporated under vacuum at room temperature and the residue was taken up in a few cc. of acetone. The solution was centrifuged free of a small quantity of insoluble material and the supernate was evaporated leaving 499 mg. of a tacky, yellow-brown solid. The latter was dissolved in 10 cc. of methanol and the solution was readily decolorized with a small quantity of charcoal (Dareo G-60). Evaporation of the methanol left 423 mg. of 5,5-dimethyl-2-phenacetylaminomethylthiazolidine-4-carboxylic acid as a pale yellow, glassy residue which was converted to a colorless powder by trituration with three 1-cc. portions of anhydrous ether. Yield, 335 mg. (11%), m.p. ca. 120°, assay <0.06 units/mg. The solubility of the substance in organic solvents was somewhat greater than that of benzylpenicilloic acid. The infrared spectrum¹⁰ exhibited only minor differences from that of benzylpenicilloic acid.

Anal. Calc'd for $C_{14}H_{20}N_2O_5$: C, 58.40; H, 6.54. Active H (3 atoms per mole), 0.98. Equiv. wt., 308.4.

Found: C, 57.03, 57.04; H, 6.76, 6.56. Active H (Zerewitinoff), 0.96, 1.00. Equiv. wt., 293; $pK_a = 4.6$.¹¹

Further preparations, by essentially the same method, did not yield more satisfactory analyses.

3,4-Dicarbanilino-5,5-dimethyl-2-phenacetylaminomethylthiazolidine (IIIa). A mixture of 201 mg. of 5,5-dimethyl-2-phenacetylaminomethylthiazolidine-4-carboxylic acid with 618 mg. of phenylisocyanate was warmed until gas evolution had ceased and then heated for one and one-half hours at 100°. The reaction mixture was triturated with six 1.5-cc. portions of ether, yielding 166 mg. of a buff-colored, partially crystalline powder; m.p. 190–195°. The infrared spectrum of the crude product indicated the absence of an appreciable quantity of *sym*-diphenylurea. Two crystallizations from absolute ethanol yielded 80 mg. of colorless needles, m.p. 200–203° (partial dec.). Following preliminary experiments, 60 mg. of the material of m.p. 200–203° was dissolved in 30 cc. of chloroform and the solution was washed with 5 cc. of 5% sodium bicarbonate and then three times with 5-cc. portions of water. Evaporation of the chloroform, after drying over anhydrous calcium sulfate, left 55 mg. of colorless residue. Crystallization of the latter from absolute ethanol yielded 53

¹⁰ For the infrared spectra reported we are indebted to Dr. R. C. Gore of the Physics Division, these Laboratories, under whose direction they were determined. Samples of 1 to 3 mg. were examined in Nujol mull as described in reference (9).

¹¹ We are grateful to Mr. J. F. Bone of the Chemotherapy Division, these Laboratories, for this titration.

mg. (22%, corrected for material removed for trial purification) of 3,4-dicarbanilino-5,5-dimethyl-2-phenacetylaminomethylthiazolidine, rosettes of colorless needles, m.p. 207–208°. The solubility behavior and infrared spectrum (Fig. 1) were identical with those of the phenylisocyanate derivative, m.p. 221–222°, from benzylpenicilloic acid. The mixed m.p. with the latter was 201–209°.

Anal. Calc'd for $C_{24}H_{30}N_4O_3S$: C, 66.91; H, 6.02; N, 11.15; S, 6.38.

Found: C, 67.18; H, 6.14, N, 11.20; S, 6.41.

α -Methyl benzylpenicilloate (VII). A solution of 202 mg. of crystalline sodium benzylpenicillin in 7.5 cc. of absolute methanol was held at reflux temperature for four hours. The solution was then evaporated in a stream of nitrogen and the residue was dried under vacuum at room temperature. A solution of the entire product in 3 cc. of water was cooled to 0° and acidified to ca. pH 2 with 1 cc. of 0.5 N sulfuric acid. The mixture was then extracted with one 2-cc. and four 0.5-cc. portions of butanol. Evaporation of the extract under vacuum left a glassy residue which was taken up in 2 cc. of acetone. The acetone solution was centrifuged clear and the supernate was evaporated leaving 204 mg. of a pale yellow glass. Trituration of the latter with 0.4 cc. of a 1:1 mixture of ether and petroleum ether yielded 198 mg. (95%) of α -methyl benzylpenicilloate as a colorless powder, m.p. ca. 75°, $(\alpha)_D^{25} + 119^\circ$ (5% sodium bicarbonate, c, 0.418), $(\alpha)_D^{25} + 94^\circ$ (abs. ethanol, c, 0.508), assay 0.27 units/mg. The substance was somewhat more soluble in organic solvents than benzyl penicilloic acid. The infrared spectra of the two were hardly distinguishable.

Anal. Calc'd for $C_{17}H_{22}N_2O_3S$: C, 55.72, H, 6.05; N, 7.65; S, 8.75. Active H (3 atoms per mole), 0.83. Equiv. wt., 366.4.

Found: C, 55.95, 56.03; H, 6.17, 5.98; N, 7.51, 7.42, S, 8.52, 8.53. Active H (Zerevitinoff), 0.84, 0.82. Equiv. wt., 365, 381; $pK_a = 3.7$.

Phenylisocyanate derivative from α -methyl benzylpenicilloate (V). A mixture of 161 mg. of α -methyl benzylpenicilloate and 419 mg. of phenylisocyanate was warmed until gas evolution has ceased, and was then heated at 80° for fifteen minutes. The reaction mixture was triturated with six 1-cc. portions of petroleum ether. The undissolved residue, after drying under vacuum, consisted of 272 mg. of light brown powder, m.p. 100–135° (dec.). Following preliminary experiments, a 238 mg. portion of the latter was triturated with one 0.5-cc. and two 0.25-cc. portions of methanol. The colorless, crystalline residue amounted to 46 mg., m.p. 125–155°. Retrituration of the tarry solid recovered from evaporation of the supernates, using one 0.25-cc. and two 0.1-cc. portions of methanol, yielded a further 56 mg. of similar material, m.p. 125–155°. Repetition of the recovery and trituration yielded 17 mg. more of material of similar appearance and m.p. The combined crude yield (119 mg.) was dissolved in 2 cc. of chloroform and the solution was allowed to stand at 0° for several hours, which effected the separation of a few mg. of *sym*-diphenylurea, m.p. 238–240°. More chloroform was added to the filtrate, bringing the volume to 4 cc. The solution was heated to boiling and 4 cc. of hexane was added. After standing in the ice box for several hours the solution yielded 47 mg. of colorless, microcrystalline powder, m.p. 160–163° (previous softening). Four further crystallizations from the same solvent-pair yielded 17 mg. (8%, corrected for material removed for trial purification) of fine, colorless needles of the phenylisocyanate derivative, m.p. 170–172°, $(\alpha)_D^{25} + 46^\circ$ (abs. ethanol, c, 0.842). A further crystallization, from acetone-hexane, prior to analysis, removed the last trace of a highly birefringent contaminant observed in the less pure fractions, but did not raise the m.p. The substance was found to be insoluble in water, 5% sodium bicarbonate, 10% sodium hydroxide, and 10% hydrochloric acid; slightly soluble in petroleum ether; moderately soluble in benzene, carbon tetrachloride, and ether; and readily soluble in chloroform, acetone, ethanol, and pyridine. The infrared spectrum (Fig. 1) differed from that of the derivative from benzylpenicilloic acid (IIIa) in being less well resolved and in having an additional absorption band at 1736 cm^{-1} (attributed to ester carbonyl).

Anal. Calc'd for $C_{26}H_{28}N_4O_3S$: C, 64.26; H, 5.75; N, 9.99; S, 5.72.

Found: C, 63.93; H, 6.24; N, 9.82, 9.92; S, 5.52.

SUMMARY

Crystalline phenylisocyanate derivatives have been prepared from 5,5-dimethylthiazolidine-4-carboxylic acid, α -methyl benzylpenicilloate, and benzylpenicilloic acid. The derivative from the latter was shown to be an optically active form of 3,4-dicarbanilino-5,5-dimethyl-2-phenacetylaminomethylthiazolidine.

STAMFORD, CONN.

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bis(*p*-NITROPHENYL) SULFIDE¹

REYNOLD C. FUSON AND S. MELAMED

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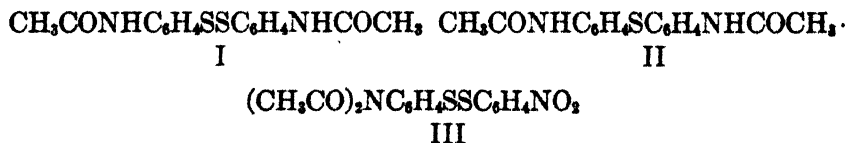
A study of *bis*(*p*-nitrophenyl) sulfide was initiated in the hope of obtaining definite information as to the possibility of the existence of thiosulfoxides—a type of derivative which had been reported for this sulfide (1) and also postulated as intermediate in the Levinstein process (2, 3). While this work was in progress Price and Stacy (4) showed that the material which had been identified by the Russian workers as *bis*(*p*-nitrophenyl) thiosulfoxide was in reality a mixture of the sulfide with the corresponding linear disulfide. The present paper is a report of certain other observations on the behavior of *bis*(*p*-nitrophenyl) sulfide.

Perhaps the most interesting of these is the reaction with sodium disulfide, discovered in an early attempt to synthesize the supposititious thiosulfoxide by heating *bis*(*p*-nitrophenyl) sulfide with sodium disulfide. Although the desired sulfurization occurred, the resulting product was not a thiosulfoxide but the well-known, linear disulfide. This reaction, involving the formation of a disulfide from a monosulfide, appears to be new in type.



Another product was *p*-nitrothiophenol, formed presumably by cleavage of the disulfide. This reaction had been carried out by Fromm and Wittmann (5) by use of alcoholic sodium hydroxide. The cleavage of disulfides by alkali has been shown to be a general reaction. Reduction of a nitro group occurred also, *p*-aminophenyl *p*-nitrophenyl sulfide being formed.

When *bis*(*p*-nitrophenyl) sulfide was treated with an excess of sodium disulfide, the disulfide was produced along with a mixture of amines. The amines were acetylated and the resulting acetyl derivatives were separated by fractional crystallization. Three amines were isolated, all containing sulfur. The first (m.p. 181–183°) was identified as *bis*(*p*-acetaminophenyl) disulfide (I) (6).



The structure was established by synthesis. *bis*(*p*-Nitrophenyl) disulfide was reduced with tin and hydrochloric acid and the resulting amino thiol was oxidized with iodine in acid solution. Acetylation of the *bis*(*p*-aminophenyl) disulfide produced a compound (m.p. 181–184°) which did not depress the melting point of the am de (m.p. 181–183°) isolated from the mixture.

¹ This paper is based on work done for the office of Scientific Research and Development under Contracts No. OEMsr-300 and OEMsr-48 with the Board of Trustees of the University of Illinois.

The second amide (m.p. 208–210°) to be isolated from the mixture appeared to be bis(*p*-acetaminophenyl) sulfide (II). This compound, which had been made previously, had the melting point 209–210°. The third amide (m.p. 212–213°) was isolated only in very small amounts and was believed to be *p*-diacetaminophenyl *p*-nitrophenyl disulfide (III).

A word should be said about the melting point of bis(*p*-nitrophenyl) sulfide. Price and Stacy gave the melting point as 160–161°, and our purest samples melted slightly lower. All previous workers had reported the value of 154° (1, 5, 7, 8). Since this compound had been prepared by so many investigators and since its identity was so essential to the original problem, a systematic examination of its structure and purity was undertaken.

The reaction of *p*-nitrochlorobenzene and sodium sulfide in ethanol solution was found to give the sulfide, unchanged *p*-nitrochlorobenzene, and *p*-aminophenyl *p*-nitrophenyl sulfide. The use of ethylene glycol as a solvent materially improved the method and led to the isolation of essentially pure sulfide as the only product. The sulfide crystallized from glacial acetic acid, xylene, or absolute ethanol in long needles. The analysis of a pure sample gave the correct values for carbon, hydrogen, and nitrogen. Results of molecular weight determinations in benzophenone afforded satisfactory checks with the calculated value (276). A determination of the nitro groups, by use of stannous chloride and iodine as reagents, gave values for "nitro" nitrogen close to the calculated value.

The reduction of bis(*p*-nitrophenyl) sulfide with tin and hydrochloric acid produced the diamino sulfide; m.p. 105–107° (7). The diacetyl derivative was prepared also; m.p. 214–215° (cor.). The preparation of *p,p'*-bis(4-nitrophenylthio)azobenzene was undertaken according to the directions of Zincke, since its melting point of 164° was so close to that found for the sulfide (8). The azo compound was isolated (m.p. 159–162°) and proved to be different from the sulfide.

Hodgson and Wilson report that the action of fused sodium sulfide on *p*-nitrochlorobenzene leads to the formation of bis(*p*-nitrophenyl) sulfide as the only product (9). We were unable to confirm these results; instead we isolated 4,4'-dichloroazobenzene (m.p. 179°) and 4,4'-dichloroazoxybenzene (m.p. 154°) from the reaction mixture. The azo compound was converted to the azoxy derivative by the action of perhydrol in glacial acetic acid. Both compounds upon treatment with fuming nitric acid gave a trinitroazoxy derivative (m.p. 186–187.5°) in which the orientation of the nitro groups was not determined. A similar result was obtained by Werigo, who oxidized the corresponding bromoazobenzene and obtained a trinitroazoxy derivative; m.p. 174° (10). Willgerodt observed the formation of 4,4'-dichloroazobenzene from *p*-nitrochlorobenzene and potassium ethoxide at 150–200° in a sealed tube (11). The reaction of *p*-dinitrobenzene and sodium sulfide was observed by Blanksma to give 4,4'-dinitroazobenzene (12). The work of Hodgson and Wilson was not supported by any experimental details, and we believe that they were in error on this point.

The reaction between sodium disulfide and 2,4-dinitrochlorobenzene proceeded readily to give a compound which had the composition calculated for *bis*(2,4-dinitrophenyl) disulfide. Oxidation of this compound gave a 5% yield of *bis*(2,4-dinitrophenyl) sulfone (13). Similar results were obtained with 2-nitro-4-carbomethoxychlorobenzene. The *bis*(2-nitro-4-carbomethoxyphenyl) disulfide melted at 149–150° and when oxidized gave an 8% yield of *bis*(2-nitro-4-carbomethoxyphenyl) sulfone (m.p. 205–206°) and an equivalent amount of sulfuric acid determined as barium sulfate. These results may be explained readily by reference to the equilibrium, $\text{Na}_2\text{S}_2 \rightleftharpoons \text{Na}_2\text{S} + \text{S}$, which probably exists under the conditions employed.

EXPERIMENTAL

Reaction of *bis*(*p*-nitrophenyl) sulfide and sodium disulfide. A solution of sodium disulfide, prepared by dissolving 0.64 g. of sulfur in a solution of 4.8 g. of sodium sulfide ($\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$) in 25 ml. of hot ethylene glycol, was added to 5.52 g. of *bis*(*p*-nitrophenyl) sulfide dissolved in 250 ml. of hot absolute ethanol. The mixture was heated under reflux for 24 hours and cooled. The solid which precipitated was washed well with ethanol, and dissolved in water. Addition of lead acetate to the aqueous solution produced a white precipitate of lead hydroxide, which dissolved upon the addition of alkali. The addition of sulfuric acid (10%) to the original solution caused the precipitation of sulfur and the evolution of sulfur dioxide. No hydrogen sulfide or sulfide ion could be detected.

The original alcohol filtrate was evaporated *in vacuo*, water was added to the residual glycol solution, and the precipitated solid (3.5 g.) was extracted with 200 ml. of hot 10% hydrochloric acid. The residue (0.6 g.), fractionated from glacial acetic acid, gave two products. The first, *bis*(*p*-nitrophenyl) disulfide, m.p. 178–180°, was purified by recrystallization from xylene. The second product melted at 135–137° after recrystallization from ethanol, and at 135–140° when mixed with a sample of the eutectic mixture of mono- and disulfides (m.p. 135–145°) (6).

The hydrochloric acid extract was made alkaline with sodium hydroxide and the amine (1.5 g.) precipitated; m.p. 137–140°. It proved to be *p*-aminophenyl *p*-nitrophenyl sulfide and was recrystallized from a mixture of benzene and petroleum ether (b.p. 60–90°).

When the aqueous-alcohol filtrate, after removal of these products, was made acidic with hydrochloric acid, a yellow solid precipitated. It was dissolved in benzene, and a small amount of insoluble material was removed. The benzene solution was extracted with 5% sodium hydroxide, and the aqueous solution treated with powdered iodine. A small yield of *bis*(*p*-nitrophenyl) disulfide was obtained, which served to identify the original material as *p*-nitrothiophenol.

Reaction of *bis*(*p*-nitrophenyl) sulfide and excess sodium disulfide. A mixture of 0.06 mole of sodium disulfide in 50 ml. of ethylene glycol and 0.02 mole of nitrophenyl sulfide in 200 ml. of absolute ethanol was heated for 20 hours, cooled, and filtered. The precipitate was completely soluble in water and proved to be sodium thiosulfate.

The filtrate was concentrated *in vacuo*, and the organic material was precipitated with water as in the previous experiment. The material (3.5 g.) was an oil and was isolated by ether extraction. The aqueous layer was acidified and extracted with ether. The product isolated was *bis*(*p*-nitrophenyl) disulfide, resulting from the air oxidation of the thiophenol.

The oil mentioned above, which was almost entirely soluble in hydrochloric acid, was purified by repeated extraction from alkaline solutions. It was treated with 10 ml. of acetic anhydride, and the mixture was warmed for 15 minutes. The product was isolated in the usual manner and was fractionated into three compounds by recrystallization from alcohol-water mixtures. The first (m.p. 181–183°) proved to be *bis*(*p*-acetaminophenyl) disulfide, identical with a sample prepared from *bis*(*p*-nitrophenyl) disulfide. The second (m.p. 208–210°) showed no depression in melting point when mixed with a sample of *bis*(*p*-acetamino-

phenyl) sulfide. The third (m.p. 212–213°) was apparently a *p*-diacetaminophenyl *p*-nitrophenyl disulfide.

Anal. Calc'd for $C_{16}H_{14}N_2O_2S_2$ (m.p. 181–183°): C, 57.8; H, 4.82; N, 8.43.

Found: C, 58.40; H, 5.10; N, 8.34.

Anal. Calc'd for $C_{16}H_{14}N_2O_2S$ (m.p. 208–210°): C, 64.00; H, 5.34; N, 9.32.

Found: C, 62.83; H, 5.28; N, 9.06.

Anal. Calc'd for $C_{16}H_{14}N_2O_4S_2$ (m.p. 212–213°): C, 53.1; H, 3.87; N, 7.74.

Found: C, 52.42; H, 4.66; N, 7.40.

Preparation of bis(p-acetaminophenyl) disulfide (m.p. 182°). To a hot solution of bis(*p*-nitrophenyl) disulfide in glacial acetic acid was added 5 ml. of concentrated hydrochloric acid and several pieces of tin. Reduction was effected by heating and by the addition from time to time of portions of acid and pieces of tin. The process was continued until all the original disulfide was dissolved, about 30 ml. of acid being required. The hot solution was filtered, and an aqueous solution of iodine and potassium iodide was added slowly until a red color persisted. The solution was cooled, and alkali was added until the precipitate of stannic hydroxide completely dissolved. The amine, extracted with ether and isolated in the usual manner, weighed 1.5 g.; it was treated with 10 ml. of acetic anhydride, and the mixture was warmed for 15 minutes. The amide was recrystallized from an acetic acid-water mixture; yield 1.2 g.; m.p. 181–184° (8). Repeated recrystallizations of the substance from ethanol-water mixtures did not change its melting point.

Preparation of bis(p-nitrophenyl) sulfide. Method I. A solution of 24 g. of sodium sulfide ($Na_2S \cdot 9H_2O$) in 150 ml. of water was added carefully, in portions, to a solution of 32 g. of *p*-nitrochlorobenzene in 100 ml. of hot absolute ethanol according to the directions of Nietzki and Bothof (9). After the initial, vigorous reaction had subsided, the mixture was heated under reflux for 6 hours. A solid and an oil separated during this period. The aqueous layer and the oil were decanted, and the residual solid was washed with alcohol and water. When recrystallized from glacial acetic acid, it formed yellow needles; m.p. 159–160°. The oil yielded the amino nitro sulfide (m.p. 143°), more of the sulfide, and some starting material. The melting point recorded by Nietzki and Bothof for the sulfide was 154° (7).

Anal. Calc'd for $C_{12}H_8N_2O_4S$: C, 52.2; H, 2.90; N, 10.1.

Found: C, 52.21; H, 2.70; N, 9.98 (separate sample).

Method II. A solution of 7.5 g. of sodium sulfide ($Na_2S \cdot 9H_2O$) in 50 ml. of ethylene glycol was added to a solution of 10 g. of *p*-nitrochlorobenzene in 25 ml. of absolute ethanol. The mixture darkened characteristically, but the reaction proceeded smoothly. The reaction mixture was heated on a steam-bath for 3 hours during which the color changed from dark red to orange, and crystals began to appear. The mixture was cooled and filtered, and the product was recrystallized from absolute ethanol. It formed beautiful, long, flat, yellow needles (m.p. 159°) identical with the substance obtained by Method I.

Determination of nitro groups in bis(p-nitrophenyl) sulfide. The reagents used were 0.1062 *N* aqueous iodine and stannous chloride solution, 35 g. in 70 g. of 25% hydrochloric acid. A sample of sulfide (0.2 g.) and 15 ml. of stannous chloride reagent were placed in a sealed tube (Pyrex) and heated in an oven at 120°, with intermittent shaking until clear. This required about 2 hours. The material was then washed into a 100-ml. volumetric flask and a 10-ml. aliquot portion was titrated with iodine to an end point, starch being used as an indicator. A blank was similarly carried through the procedure. The calculations were made on the basis of 1 ml. of 0.1 *N* $I_2 \approx 0.0002335$ g. of N_2 present in the nitro group. The results were as follows: Calc'd for $NO_2C_6H_4SC_6H_4NO_2$: N, 10.1. Found: (Sample I) N, 9.84; (Sample II) N, 10.36.

Reduction of bis(p-nitrophenyl) sulfide (9). A 2-g. sample of the sulfide was dissolved in a mixture of glacial acetic and hydrochloric acids. Small pieces of tin were added and the mixture warmed until all the material was in solution. The mixture was filtered and the amine isolated in the usual manner. The amine was recrystallized from a mixture of benzene and petroleum ether and had the melting point 105–107°. The melting point of bis(*p*-aminophenyl) sulfide is 108°.

Attempts to prepare a sulfonium salt of bis(p-nitrophenyl) sulfide. A solution of 0.5 g. of

sulfide in chloroform was treated with 0.23 g. of methyl sulfate under reflux for one-half hour. Only the original sulfide was obtained.

One gram of sulfide was dissolved in 10 ml. of methyl sulfate and heated at 100°, under a reflux condenser protected by a calcium chloride tube, for 96 hours. The mixture was diluted with water and filtered; the residue was unchanged sulfide. The filtrate was treated with mercuric chloride solution, shaken well, and allowed to stand overnight. A small amount of tan precipitate formed; it was recrystallized and proved to be the original sulfide; m.p. 158–160°.

Reaction of p-nitrothiophenol and p-nitrochlorobenzene. The *p*-nitrothiophenol was prepared from 32 g. of *p*-nitrochlorobenzene according to the directions of Bennett and Berry (14). The solution of the sodium salt in 150 ml. of water was added to a solution of 15 g. of *p*-nitrochlorobenzene in 100 ml. of alcohol, and the mixture was heated under reflux until the red color lightened. The reaction product was a difficultly separable mixture from which were isolated *p*-aminophenyl *p*-nitrophenyl sulfide, *p*-nitrochlorobenzene, and a small amount of *bis*(*p*-nitrophenyl) sulfide.

Preparation of p,p'-bis(4-nitrophenylthio)azobenzene (10). A mixture of 10 g. of *bis*(*p*-nitrophenyl) disulfide, m.p. 181°, dissolved in 150 ml. of alcohol and a solution of 6 g. of sodium hydroxide, dissolved in 30 ml. of water was heated for 20 minutes. The mixture was cooled, diluted with 1500 ml. of water, and filtered. The precipitate was extracted with hot hydrochloric acid. The residue, after recrystallization from glacial acetic acid, melted at 159–163°. A mixture of this compound and *bis*(*p*-nitrophenyl) sulfide melted at 135–140°. Repeated recrystallizations from benzene and acetic acid gave well-formed crystals; m.p. 159–162°. The melting point of the azobenzene is given as 164° (7, 10).

Preparation of p,p'-dichloroazoxybenzene. Six grams of *p*-nitrochlorobenzene was added to 20 g. of sodium sulfide ($\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$) which had been heated at 110° for one hour, and the mixture was heated at 100° for 20 hours. The deep red mass was treated with 50 ml. of absolute ethanol and filtered. The precipitate was washed well with water and recrystallized from a small amount of glacial acetic acid. After several recrystallizations about 0.5 g. of *p,p'*-dichloroazoxybenzene was obtained; m.p. 154°.

Anal. Calc'd for $\text{C}_{12}\text{H}_8\text{Cl}_2\text{N}_2\text{O}$: C, 54.00; H, 3.00.

Found: C, 54.03; H, 2.81.

Preparation of p,p'-dichloroazobenzene. Two hundred grams of powdered sodium sulfide ($\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$) was heated in an oil-bath at 110° for several hours while being agitated mechanically. To the solution was added 60 g. of *p*-nitrochlorobenzene, and the mixture was stirred and heated at 100° for 20 hours. The contents of the flask were cooled, diluted with 500 ml. of water, and filtered. The precipitate was extracted with hot 10% hydrochloric acid, and the residue was recrystallized several times from glacial acetic acid. The product was obtained as orange-yellow plates; m.p. 177–179°. The melting point of *p,p'*-dichloroazobenzene as recorded in the literature is 183° (15). An elementary analysis gave positive tests for nitrogen and chlorine, negative results for the sulfur.

Anal. Calc'd for $\text{C}_{12}\text{H}_8\text{Cl}_2\text{N}_2$: C, 57.40; H, 3.18.

Found: C, 56.77; H, 3.05.

Nitration of p,p'-dichloroazobenzene. About 0.5 g. of the azo compound was treated carefully with 3 ml. of nitric acid (sp. gr. 1.5), and the mixture was heated on a steam-bath for one hour. A yellow precipitate, obtained by dilution of the mixture with water, was recrystallized from glacial acetic acid; m.p. 186–187°. After a second treatment with 3 ml. of nitric acid, the product melted at 186–187.5°.

Anal. Calc'd for $\text{C}_{12}\text{H}_6\text{Cl}_2\text{N}_2\text{O}_7$: C, 35.70; H, 1.24; N, 17.4.

Found: C, 36.28; H, 1.59; N, 16.59.

Nitration of p,p'-dichloroazoxybenzene. A 0.5-g. sample of the azoxy compound was oxidized with nitric acid (sp. gr. 1.5) according to the procedure for the related azo compound. The product was yellow; m.p. 186–187°. A mixture with the nitration product of *p,p'*-dichloroazobenzene had the melting point 186–187°.

Perhydrol oxidation of 4,4'-dichloroazobenzene. A small sample of the azo compound was dissolved in glacial acetic acid and 10 ml. of perhydrol (30%) was added over a period of 5

hours to the hot solution (16). The solution changed from an orange color to a light yellow. The heating was continued for 8 hours, and the mixture was cooled and diluted with water. The solid, when collected and recrystallized from an aqueous-ethanol mixture, formed crystals (m.p. 154–156°) identical with the 4,4'-dichloroazoxybenzene isolated previously.

Preparation of *p*-aminophenyl *p*-nitrophenyl sulfide (9). A solution of 32 g. of *p*-nitrochlorobenzene in 100 ml. of absolute ethanol was placed in a 500-ml., round-bottomed flask equipped with a long, efficient condenser, and the solution was heated almost to boiling on a steam-bath. To this hot solution was added, in small portions through the condenser, a solution of 24.0 g. of sodium sulfide ($\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$) in 150 ml. of water. After the mixture had been heated for one hour, a solution of 8 g. of sodium sulfide in 30 ml. of water was added, and the mixture heated under reflux for 10 hours.

When the reaction was complete there were present an aqueous-alcohol layer, an oil, and a solid. The products of two similar experiments were combined. The hot solvent and the oil were decanted from the solid, and the solid was washed with alcohol and recrystallized from glacial acetic acid; m.p. 158–159°. This compound was identical with an authentic sample of bis(*p*-nitrophenyl) sulfide. The remainder of the reaction mixture was cooled well, and the solid was collected by filtration, the filtrate being discarded.

The solid material was placed in a flask together with 50 ml. of concentrated hydrochloric acid and 300 ml. of water, and the mixture subjected to steam distillation until 1200 ml. of distillate had been collected. When cooled, the distillate yielded 3 g. of *p*-nitrochlorobenzene. The mixture in the flask was filtered while hot, the filtrate being a clear yellow liquid. The residual solid was a mixture, difficult to separate, and consisting mostly of the sulfide mentioned above.

The filtrate was cooled and neutralized with sodium hydroxide. The amine was removed by filtration and recrystallized from a mixture of benzene and petroleum ether (b.p. 60–90°); m.p. 138–142°; yield 4 g.

Preparation of bis(2,4-dinitrophenyl) disulfide. The directions of Blanksma (12) were followed, 13.3 g. of 2,4-dinitrochlorobenzene, 8 g. of sodium sulfide ($\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$), and 1.0 g. of sulfur being used. The crude product (12 g.) was washed well with water and alcohol.

Anal. Calc'd for $\text{C}_{12}\text{H}_6\text{N}_4\text{O}_8\text{S}_2$: C, 36.2; H, 1.51.

Found: C, 36.45; H, 1.47.

Oxidation of the bis(2,4-dinitrophenyl) disulfide mixture. A 4-g. sample of the crude mixture obtained in the preceding experiment was oxidized with 15 ml. of nitric acid (sp. gr. 1.5) in the usual manner. The reaction mixture was diluted with 60 ml. of water, and the precipitated solid collected and dried, yield, 0.245 g. Several recrystallizations from glacial acetic acid gave white needles (m.p. 240–241°), corresponding to the literature value (240°) for bis-2,4-dinitrophenyl sulfone (17). The filtrate after removal of the sulfone was evaporated *in vacuo*. The residue solidified and was easily soluble in water. Neutralization of the aqueous solution with potassium carbonate gave yellow crystals of the potassium salt of 2,4-dinitrophenylsulfonic acid. The crystals exploded with a purple flame on ignition.

Preparation of bis(2-nitro-4-carbethoxyphenyl) disulfide. The procedure of Blanksma for the preceding disulfide was followed, 10.8 g. of 2-nitro-4-carbomethoxychlorobenzene, 6 g. of sodium sulfide ($\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$), and 0.8 g. of sulfur being allowed to react in absolute ethanol. The mixture was heated for 15 minutes, and the product recrystallized from ethanol. The solid had the composition of bis(2-nitro-4-carbethoxyphenyl) disulfide, m.p. 149–150°, transesterification evidently having occurred.

Anal. Calc'd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_8\text{S}_2$: C, 47.80; H, 3.54.

Found: C, 47.76; H, 3.61.

Oxidation of the bis(2-nitro-4-carbethoxyphenyl) disulfide mixture. A 4-g. sample was oxidized in the usual way. The solid obtained on dilution weighed 0.35 g. and had a composition corresponding to that of bis(2-nitro-4-carbethoxyphenyl) sulfone; m.p. 205–206°.

Anal. Calc'd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_{10}\text{S}$: C, 47.80; H, 3.54.

Found: C, 49.50; H, 3.70.

The filtrate, when treated with a solution of barium chloride, gave 0.23 g. of barium sulfate, which did not darken or burn on ignition.

SUMMARY

bis(p-Nitrophenyl) sulfide has been found to undergo sulfurization when heated with sodium disulfide, yielding *bis(p*-nitrophenyl) disulfide. This reaction, the formation of a disulfide by sulfurization of the corresponding monosulfide, appears to be new in type.

The disulfides prepared from 2,4-dinitrochlorobenzene and 2-nitro-4-carbomethoxychlorobenzene by the action of sodium disulfide appeared to be contaminated with the corresponding monosulfides. In each case oxidation gave small amounts of sulfone.

URBANA, ILLINOIS

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5-METHYLDOISYNOLIC ACID AND 1-METHYLESTRONE

CARL DJERASSI AND CAESAR R. SCHOLZ

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In 1940, Inhoffen (1) reported that 1-methylestradiol (I), prepared by the dienone-phenol rearrangement of 1,4-androstadien-17-ol-3-one (2) was estrogenically inactive in doses up to 1 mg. in rats, *i.e.* nearly ten thousand times the threshold dose of the female sex hormone estradiol (II). In view of the rather large number of diverse compounds which exhibit estrogenic activity, it is rather surprising that the introduction of a methyl group into the aromatic ring of estradiol should abolish completely the biological activity. Inhoffen offered this explanation: "Without doubt, the physiological inactivity is connected with the diminished solubility in alkali, and the latter is evidently a result of the 1-methyl group." In connection with a related problem, we have improved the synthesis of 1-methylestradiol (3) and have been able to substantiate fully Inhoffen's report regarding the loss in physiological activity. However, his explanation of this phenomenon seems to us to be over-simplified, particularly since the alkali-soluble 5-methyldoisynolic acid, to be discussed below, is also devoid of estrogenic potency.

It is an experimental fact that 1-methylphenols of the steroid series behave like pseudo-phenols in that they are insoluble in aqueous alkali, but it is difficult to understand how this alkali-insolubility *per se* should have physiological significance in the intact animal. While the mode of action of the estrogens in the body is as yet not understood, a more probable explanation for the inactivity of 1-methylestradiol appears to us to be a steric effect of the 1-methyl group and/or the low acidity of the phenolic group of 1-methylestradiol interfering with an essential metabolic step, such as an enzyme-coenzyme relationship, which thus is intimately connected with the nature of ring A. It seemed to us of interest to investigate the generality of this phenomenon since it might have some bearing on the biochemical function of the estrogens.

Doisy and co-workers (4) and later Heer and Miescher (5) have demonstrated that estradiol (II) could be converted by alkali fusion to an estrogenically highly potent acid (IV), recently termed doisynolic acid. By applying the same method to 1-methylestradiol (I), we have isolated an alkali-soluble monocarboxylic acid, still possessing the typical ultraviolet absorption spectrum of a phenol and which by analogy to the work of Heer and Miescher (5) is considered to be 5-methyldoisynolic acid (III). This acid proved to be inactive¹ in rats when injected in nearly one thousand times the active dose of doisynolic acid (6). This would in

¹ "Inactivity" in this paper refers to a lack of response in the vaginal smear test in rats (administered in oil solution), so as to be comparable to Inhoffen's results (1, 2) with 1-methylestradiol.

dicates that also in the doisyolic acid series the nature of ring A is an important factor for estrogenic activity. In addition, we have prepared 1-methylestrone (Va) by a method to be discussed below and have found this substance to be inactive in 0.5-mg. doses (higher levels have not been tested since estrone is active in 0.001-mg. doses). The theoretical implications are not clear at present, but it should be noted that in any future hypothesis on the mode of action of the estrogens, the unusual effect of methyl substitution in the aromatic ring of estrone, estradiol, and doisyolic acid will have to be considered.²

In their report on the synthesis of 1-methylestradiol (I), Inhoffen and Zuehlendorff (2) in a footnote mentioned that they had prepared 1-methylestrone (Va) by the usual method [methyl migration in acetic anhydride-sulfuric acid solution, subsequently termed (7) the "dienone-phenol rearrangement"] from impure 1,4-androstadiene-3,17-dione (IX) which in turn had been obtained from impure 2,4-dibromoandrostane-3,17-dione (VIII). Except for the melting point, no details as to yield, analysis, biological activity etc. were reported.

To prepare 1-methylestrone (Va) by the dienone-phenol rearrangement, it was necessary to synthesize 1,4-androstadiene-3,17-dione (IX). Two obvious syntheses were available. One involves Oppenauer oxidation of the corresponding hydroxy compound, 1,4-androstadien-17-ol-3-one, which subsequently has been carried out successfully by Inhoffen and co-workers (8). However, at least eight separate steps from dehydroisoandrosterone acetate are necessary to prepare the starting material for the oxidation (2, 3). A much shorter synthesis from dehydroisoandrosterone acetate is outlined in the accompanying flowsheet and involves the dibromination of androstane-3,17-dione (VI). This synthesis was attempted already in 1937 (9), but neither pure nor crystalline products were isolated (1).

As was stated at that time, the main difficulty was encountered in isolating a homogeneous dibromo derivative and dehydrobrominating the latter. Continuing our recent study of the bromination of 3-keto *allosteroids*, in which we employed extensively polarimetric procedures (10, 11), we have applied successfully those methods to the dibromination of the diketone VI.

In the dibromination of 3-keto *allosteroids* which possess no other groups reactive towards bromine, it has been shown (10) that the primary product was always the 2,2-dibromo derivative, which could be rearranged, either separately or *in situ* to the 2,4 isomer (*cf.* 14). In the case of androstane-3,17-dione (VI) however, the following dibromo derivatives are theoretically possible: 2,2; 2,4; 2,16; 16,16. Since it has been demonstrated (12) that the monobromination of VI results in preferential attack of C-2, only the first three dibromo compounds

² It is of interest to note that 3,4-bis(4-hydroxy-2,5-dimethylphenyl)hexane and the corresponding hexadiene derivative (Niederl, Weiss, and Van Meter, Abstracts p. 28K, A.C.S. Meeting, New York City, Sept. 1947) are soluble in 5% sodium hydroxide solution and are fully active in 5 γ doses (J. B. Niederl, private communication). These compounds appear to be the closest analogs to 1-methylestradiol among the synthetic estrogens, but it is open to question whether on the basis of the superficial structural resemblance [see Koch, *Nature*, **161**, 309 (1948)] one can state that the estrogenic effect persisted because the synthetic phenols were sufficiently acidic.

mentioned above should be encountered. Dannenberg (13) in a study of the dibromination of androstane-3,17-dione considered only the possibility of 2,4 and 2,16 isomers, since at that time 2,2-dibromo derivatives had not been described as yet. Of the products isolated, the structure of the 2,16-dibromo derivative was proved by an independent and unequivocal method of synthesis, and thereby was noted the considerably lower reactivity of C-16 towards bromine as compared to the *alpha* positions in ring A (C-2 and C-4). A second dibromo compound of nearly the same melting point and rotation as the 2,16 isomer was obtained, but it gave a definite depression in a mixed melting point determination,

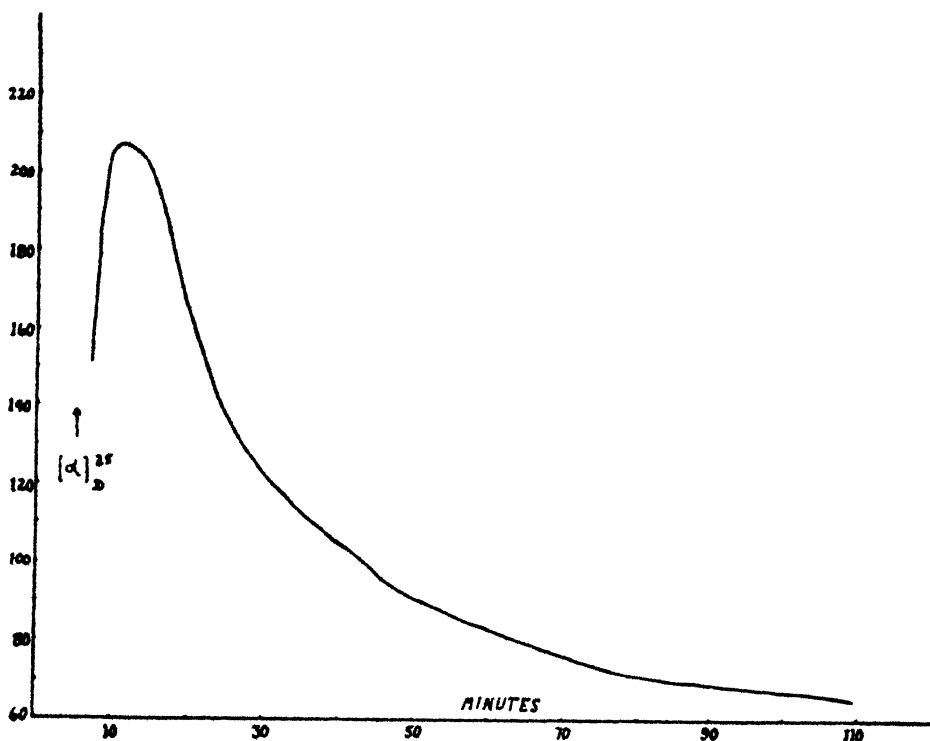


FIG. 1. POLARIMETRIC INVESTIGATION OF THE DIBROMINATION OF ANDROSTANE-3,17-DIONE (VI).

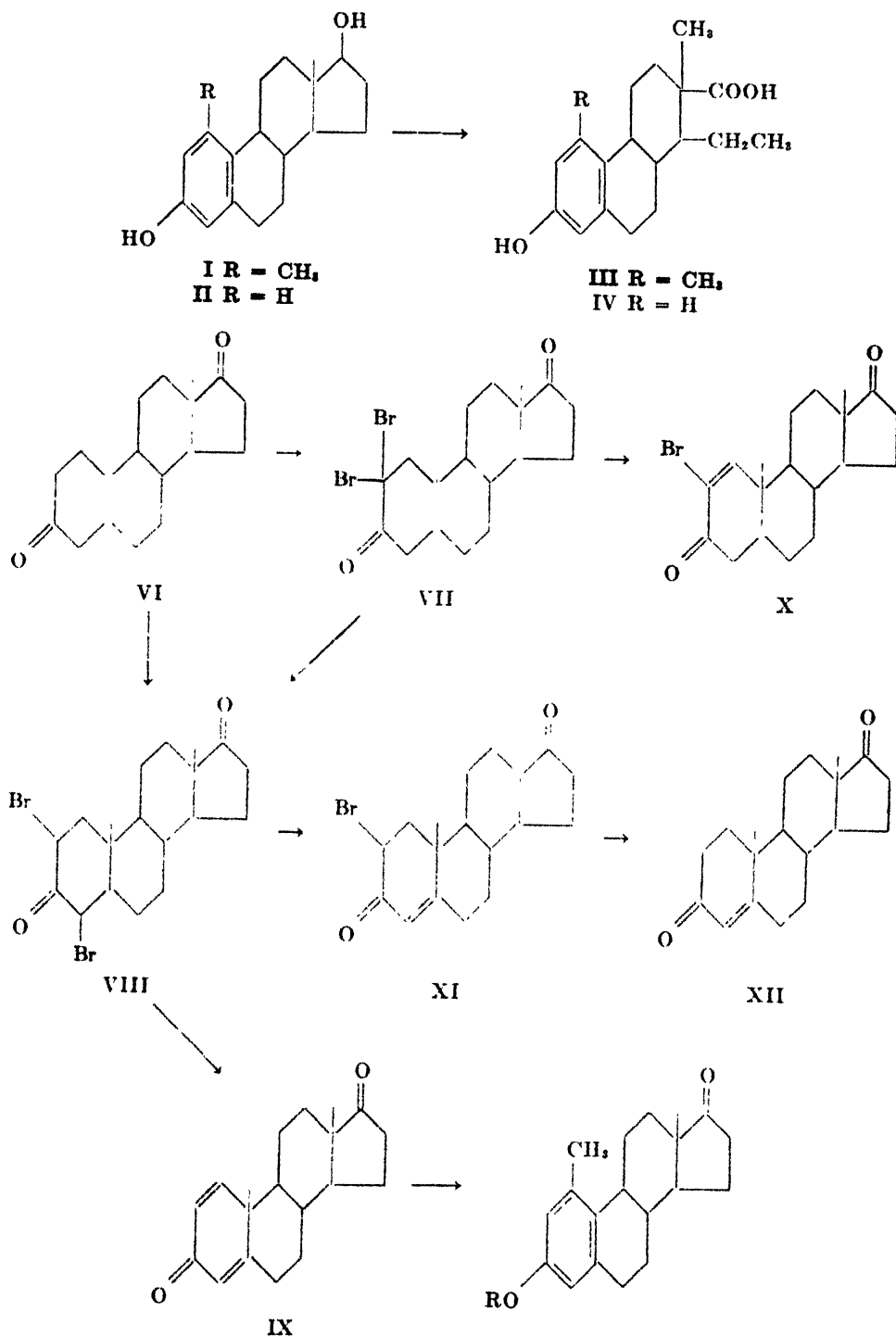
and was believed to be the 2,4 isomer. The structure of the latter could not be proved by dehydrobromination since the use of collidine had as yet not been introduced; in addition the presence of tribromo and possibly also other derivatives was noted.

In view of the rapid formation of the 2,2-dibromo compounds (10) in contrast to the relatively sluggish bromination of the 17-ketones (13), the structure VII suggested itself for the primary product. When the dibromination of VI was investigated in the polarimeter, the typical curve (Fig. 1) was observed showing an early maximum in rotation indicative of the formation of the 2,2 isomer. The end product (after complete rearrangement) showed a rotation of $+40^\circ$, in ex-

cellent agreement with the value reported by Dannenberg (13). Furthermore, on applying the method of molecular rotation differences, a $\Delta[M]_D$ value of -124° is obtained, which falls well within the experimental limit of the observed $\Delta[M]_D$ value of -136° reported for the 2,4-dibromo-3-keto *allosteroids* (11). Since Dannenberg's (13) 2,16 isomer showed the same rotation and nearly identical decomposition point, additional chemical evidence was necessary to prove the structure of the above compound as VIII. This was accomplished by dehydrobromination with collidine, yielding the desired 1,4-androstadiene-3,17-dione (IX). In agreement with earlier work on related 2,4-dibromo ketones (10, 14), it was also possible to dehydrobrominate VIII selectively by short treatment with collidine affording the monobromo derivative XI, which exhibited the typical absorption spectrum of a Δ^4 -3-keto steroid (maximum at 243 mu). Its structure was confirmed further by debromination to Δ^4 -androstene-3,17-dione (XII).

Attempts to isolate the pure 2,2-dibromo isomer (VII) were not completely successful. Judging from the results obtained in the polarimetric study of the dibromination (Fig. 1), the highest rotation ($[\alpha]_D +207^\circ$) corresponds to a $\Delta[M]_D$ value of -623° , but when the solution was diluted at the time it reached this maximum rotation and the precipitate isolated, it showed only a rotation of $+158^\circ$ ($\Delta[M]_D +403^\circ$), which was somewhat beyond the experimental limit for the observed $\Delta[M]_D$ value of $+459^\circ$ for 2,2-dibromo ketones (11); the lower value is due to the presence of small amounts of tribromo and probably also 2,4-dibromo compounds present as impurities. No obvious explanation is evident for the abnormally high rotation of the initial reaction mixture; nevertheless there is no doubt that it contained predominantly the 2,2-dibromo isomer as proved by the formation of the 2,4 derivative VIII in high yield on rearrangement and by dehydrobromination to the Δ^1 -2-bromo derivative X with its typical maximum at 256 mu (10). It is quite clear that the difficulties encountered by the previous investigators (1, 13) in obtaining the desired 2,4-dibromo derivative VIII in a pure state lay in the fact that they diluted the reaction mixture at the point of decolorization and thus had to separate a mixture of 2,2 and 2,4 isomers. The properties of the by-product mentioned by Dannenberg (13) resemble those of the 2,2-dibromo compound VII, although no rotation was reported. By the method described in the experimental section, the desired dibromo compound VIII can be obtained directly from VI in about 90-95% yield in satisfactory purity for the dehydrobromination.

The dienone-phenol rearrangement of the dienone IX to yield the desired 1-methylestrone (Va) was attempted first in acetic anhydride solution containing sulfuric acid, a method which has been successful in a number of dienones with varying substituents at C-17. However, in the first runs none of the desired material was isolated, and it was noted that the entire product of the reaction was water-soluble. Windaus and co-workers (17, 18) have shown that steroid ketones such as cholestenone or coprostanone are readily sulfonated at room temperature with sulfuric acid in acetic anhydride solution, conditions which are nearly identical with those of the dienone-phenol rearrangement. It was, therefore, suspected that sulfonation had occurred at C-16, since the dienone IX differs



only in a C-17 carbonyl group from the other steroid dienones which can be rearranged under those conditions without sulfonation (2, 3, 10, 15, 16). For instance, the corresponding compound with a C-17 hydroxyl group, on treatment with 1.5 moles of sulfuric acid, gave 71% of the corresponding phenol (3) while in the present case under the same conditions *none* of the phenol was isolated. The ease of sulfonation of 17-keto steroids was demonstrated when it was found possible to sulfonate estrone, isoandrosterone acetate etc., with one mole of sulfuric acid in acetic anhydride, sulfonation occurring *alpha* to the ketone group. These sulfonation studies as well as the isolation of 1-methylestrone-16-sulfonic acid from the rearrangement will be described in a forthcoming publication in this journal.

The rearrangement could be carried out in 80% yield by using *p*-toluenesulfonic acid; by limiting the amount of sulfuric acid considerably it was also possible to isolate 1-methylestrone (Va) although in lower yield. The reduction of the keto group of Va with lithium aluminum hydride (20) afforded 88% of 1-methylestradiol (I), which represents a considerable simplification of the earlier synthesis involving 1,4-androstadien-17-ol-3-one (2, 3).

Acknowledgment. The authors would like to express their gratitude to Jean Rogers and Helen Dudek for their skillful assistance. Elizabeth Ryan was responsible for most of the rotations and absorption spectra, and Greta Holmquist carried out all of the biological assays.

EXPERIMENTAL³

5-Methylidoisynolic acid (III). The procedure described below was adapted from the one of Heer and Miescher (5) for the fusion of estradiol.

A mixture of 0.5 g. of 1-methylestradiol (2, 3), 25 g. of potassium hydroxide pellets, and 4 cc. of water was fused in an open crucible with occasional stirring for thirty minutes in a metal-bath maintained at 350–370°, a slow current of nitrogen being passed over the surface of the reaction mixture. The cooled melt was taken up in water, acidified, extracted with ether, and the organic layer was extracted several times with 5% potassium hydroxide solution. The combined basic solutions were acidified with concentrated hydrochloric acid and the product was extracted with ether. After washing with a few cc. of sodium bicarbonate solution to remove colored impurities, the ether solution was washed with water, dried, and evaporated. The residue crystallized on trituration with hexane to yield 0.23 g. (43%) of light tan crystals ranging in m.p. (in two separate experiments) from 144–148° to 149–155°; (Found: C, 75.66; H, 8.56). After several recrystallizations from a mixture of hexane and acetone, 5-methylidoisynolic acid (III) crystallized as colorless, minute octahedra with m.p. 154–156° (cloudy, clearing at 162°), $[\alpha]_D^{25} +161^\circ$. The ultraviolet absorption spectrum was practically identical with that of doisynolic acid (5), maximum at 285 mμ, log E 3.15, minimum at 249.5 mμ, log E 2.13.

Anal. Calc'd for $C_{19}H_{24}O_4$: C, 75.46; H, 8.66; neutral equiv., 302.

Fonnd: 75.36; H, 8.81; neutral equiv., 299.

Dibromination of androstane-3,17-dione. The polarimetric study was carried out exactly

³ All melting points below 220° are corrected. Rotations were determined on 5–10 mg. of sample in 1.2 cc. of chloroform in a 1 dm. tube of 1 cc. capacity. Absorption spectra measurements were carried out in 95% ethanol solution. The microanalyses were carried out by Mr. Joseph F. Alicino, Metuchen, N. J. and Mr. George L. Stragand, Microchemical Laboratory, University of Pittsburgh.

as described in our earlier paper (10) using 144 mg. of androstane-3,17-dione (VI), 15.00 cc. of Baker C.P. glacial acetic acid and 2.50 cc. of standard bromine-acetic acid solution (1.6 g. in 25 cc.). The results are shown in Fig. 1 and demonstrate clearly the intermediate formation of a 2,2-dibromo derivative.

(a) *Isolation of 2,2-dibromoandrostane-3,17-dione* (VII). The reaction was carried out in a polarimeter tube, but the solution was poured immediately into water when the rotation had reached its highest value ($[\alpha]_D^{25} + 207^\circ$). After cooling in ice, the crystals were filtered, washed thoroughly with water, and dried; yield 90%, m.p. 135–170° (dec.), $[\alpha]_D^{25} + 144.3^\circ$ (chloroform), (Found: Br, 37.72). Recrystallization from ethanol gave crystals of m.p. 133–135° (dec.), $[\alpha]_D^{25} + 147.9^\circ$.⁴ In another run, where the product was precipitated only partially with water so as to obtain two fractions, the first crop had m.p. 179–183° (dec.) $[\alpha]_D^{25} + 153^\circ$, and the second crop showed m.p. 124–178° (dec.) $[\alpha]_D^{25} + 84^\circ$. Recrystallization of the first fraction from ethanol gave crystals with the following properties: m.p. 148–150° (dec.), $[\alpha]_D^{25} + 157.9^\circ$ (chloroform).

Anal. Calc'd for $C_{19}H_{26}Br_2O_2$: C, 51.14; H, 5.87; Br, 35.82.

Found: C, 49.67; H, 5.63; Br, 37.63.

The significance of the above rotation values in terms of molecular rotation differences is given in the discussion. It is clear that the material consists to a large extent of the 2,2-dibromo isomer, contaminated by some tribromo and possibly also 2,4-dibromo derivative. The mixture⁵ does not seem to be amenable to complete separation by crystallization, but the presence of the 2,2 isomer was demonstrated by dehydrobromination to the Δ^1 -2-bromo compound X, and by the high yield obtained in the direct preparation of the 2,4-dibromo compound [see (b)] in which the 2,2 isomer is an intermediate (10).

(b) *Isolation of 2,4-dibromoandrostane-3,17-dione* (VIII). This compound has already been prepared in unspecified yield by Dannenberg (13) by dibromination of VI in acetic acid and immediate precipitation with water at the point of decolorization. Although not realized at the time, such a procedure always results in mixtures contaminated by varying amounts of 2,2-dibromo derivative (10). Taking into account the intermediate formation of this isomer and the results of the polarimetric measurements, the following method was developed and has given excellent yields.

A solution of 1 g. of androstane-3,17-dione in 10 cc. of C.P. glacial acetic acid (water content not above 35 mg./10 cc., see ref. 10) was treated at room temperature⁶ with 0.2 cc. of 4 N hydrogen bromide-acetic acid solution followed by 17.4 cc. of standard bromine-acetic acid solution. After decolorization, which was almost instantaneous, the solution was warmed to about 50° and stoppered. Crystals of the 2,4-dibromo compound VIII appeared within a few minutes, particularly when seed crystals were added, and after standing at room temperature (25°) for three and one-half hours, the solution was cooled for one-half hour, the crystals collected and washed well. The yield of 2,4 isomer was 68–71% of material with $[\alpha]_D^{25} + 38^\circ$ to 44° . The decomposition point varied between 182° and 187°, but this material was satisfactory for the next step. Dilution of the filtrate gave an additional 22–30% of material of m.p. 179° (dec.) which was satisfactory for the dehydrobromination step if the

⁴ It was found that the rotation of the 2,2-dibromo compound was nearly the same in acetic acid as in chloroform and that it did not change on standing. This observation excludes, therefore, the possibility that a change in solvents was responsible for the difference of the two rotations observed ($[\alpha]_D^{25} + 207^\circ$ in the polarimeter as compared to $+150^\circ$ to 158° of the sample isolated).

⁵ Such a mixture was encountered already by Dannenberg (13) although he did not realize the presence of the 2,2-dibromo compound.

⁶ This is in contrast to the dibromination of androstan-17-ol-3-one 17-hexahydrobenzoate (10), where the solution was warmed first so as to catalyze both the bromination and rearrangement. In the present case, advantage is taken of the lowered reactivity of the C-17 carbonyl group and the bromination is carried out at room temperature to avoid as much as possible reaction at C-16, and the solution is warmed only at the point of decolorization to facilitate the rearrangement of the 2,2 to the 2,4 isomer.

androstanedione used was of good grade (m.p. 132–133°). Otherwise, this crop had to be recrystallized.

After several recrystallizations from chloroform-ethanol, the analytical sample had m.p. 209–210° (dec.) when immersed into the bath at 200°, $[\alpha]_D^{25} + 39.8^\circ$. Dannenberg reported m.p. 223–225° (dec. uncorr.), $[\alpha]_D^{25} + 41.5^\circ$. In our experience, the decomposition point was not a very reliable criterion.

Anal. Calc'd for $C_{19}H_{28}Br_2O_2$: C, 51.14; H, 5.87; Br, 35.82.

Found: C, 51.23; H, 5.77; Br, 35.39.

Δ^1 -2-Bromoandrosterone-3,17-dione (X). To demonstrate the presence of the 2,2-dibromo structure in the dibromo derivative of $[\alpha]_D^{25} + 157.9^\circ$ obtained above (a), 0.25 g. of the compound was refluxed with 1 cc. of collidine for ten minutes. The collidine hydrobromide weighed 151 mg. and corresponded to 1.34 moles of hydrogen bromide. The collidine solution was worked up in the usual manner, yielding an oil which on crystallization from hexane gave 0.12 g. (59%) of crystals melting at 142–160° (Found: Br, 20.57) and showed a single maximum at 255 mu, characteristic for Δ^1 -2-bromo-3-keto steroids (10). Complete purification could be accomplished only by chromatographing and entailed considerable loss of material. The analytical sample crystallized from hexane-acetone as colorless, prismatic needles of m.p. 175–177°, $[\alpha]_D^{25} + 84.9^\circ$. The ultraviolet absorption spectrum exhibited a maximum at 256 mu, log E 3.84 and a minimum at 215 mu, log E 3.30.

Anal. Calc'd for $C_{19}H_{24}Br_2O_2$: C, 62.47; H, 6.90; Br, 21.88.

Found: C, 62.40; H, 6.92; Br, 21.68.

1,4-Androstadiene-3,17-dione (IX). When 1 g. of the 2,4-dibromo derivative (unrecrystallized) was refluxed with 4 cc. of collidine for one-half hour, 0.95 g. of collidine hydrobromide was formed. Since this was in excess of the theoretical amount (0.905 g.) for two moles of hydrogen bromide, it afforded further indication that small amounts of tribromo derivative are formed during the dibromination. The collidine filtrate was worked up as usual (including chromatography, see ref. 15) and afforded 54% of crude crystalline material of m.p. 104–126°, maximum at 244 mu, which could be used for the dienone-phenol rearrangement. The compound had a great tendency to oil out, but the analytical sample was obtained as large, colorless rectangular plates on careful cooling of a hexane-acetone solution; m.p. 140–141°, $[\alpha]_D^{25} + 118.8^\circ$. Inhoffen and co-workers (8) prepared this compound in 56% yield by Oppenauer oxidation of 1,4-androstadien-17-ol-3-one and reported m.p. 139–140°, $[\alpha]_D^{25} + 115.8^\circ$ (chloroform). The present synthesis is superior in terms of availability of starting material, over-all yield, and number of steps.

Anal. Calc'd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51.

Found: C, 80.15; H, 8.36.

Δ^1 -2-Bromoandrosterone-3,17-dione (XI). Previous reports (10, 14) have shown that the bromine atom at C-4 of 2,4-dibromo-3-keto *allosteroids* can be removed selectively in the form of hydrogen bromide by short collidine treatment. This has been applied to 2,4-dibromoandrosterone-3,17-dione (VIII) as additional proof of structure.

After refluxing 1.5 g. of VIII in 6 cc. of collidine for thirty seconds, the collidine hydrobromide was filtered (0.98 g., equivalent to 1.45 moles of hydrogen bromide), the collidine filtrate was diluted with ether, washed with acid, and the ether dried and evaporated. The nearly colorless residue was recrystallized several times from a mixture of hexane and acetone to give 39% of rosettes of thin needles with m.p. 167–168° (dec.), $[\alpha]_D^{25} + 170^\circ$, maximum at 243 mu, log E 4.07.

Anal. Calc'd for $C_{19}H_{24}BrO_2$: C, 62.47; H, 6.90; Br, 21.88.

Found: C, 62.35; H, 6.77; Br, 22.58.

Debromination of Δ^1 -2-bromoandrosterone-3,17-dione (XI). Debromination was accomplished by treating 150 mg. of the unsaturated bromo derivative XI in 10 cc. of acetone with 6 cc. of chromous chloride solution (19) for two hours in a carbon dioxide atmosphere. After dilution with water and extraction with ether, there was obtained 70 mg. (57%) of bromine-free, colorless crystals of m.p. 168–170°, $[\alpha]_D^{25} + 186.5^\circ$, which gave no depression in melting point on admixture with authentic Δ^1 -androsterone-3,17-dione (XII) (m.p. 170–171°).

1-Methylestrone (Va). (a) *With sulfuric acid.* A solution of 200 mg. of 1,4-androstadiene-3,17-dione (m.p. 138–140°) in 7 cc. of acetic anhydride was treated with one drop (25 mg.) of concentrated sulfuric acid and the light tan colored solution was allowed to stand at room temperature for five hours. Water was added to hydrolyze the acetic anhydride, the oily acetate was extracted with ether, washed with sodium hydroxide and water, and the ether was evaporated. The oil was refluxed for one hour with 500 mg. of potassium hydroxide and 10 cc. of methanol and acidified with 5% aqueous hydrochloric acid. The pale yellow crystals were filtered and dried; yield 80 mg. (40%), m.p. 235–242°, $[\alpha]_D^{25} + 266^\circ$. Recrystallization from ethanol gave colorless needles with m.p. 249–251°, $[\alpha]_D^{25} + 271.6^\circ$. The absorption spectrum was practically identical with that of 1-methylestradiol (2,16), maximum at 282.5 mμ, log E 3.37, minimum at 249 mμ, log E 2.15. Inhoffen and Zuehlisdorff (2) reported m.p. 247–249° for 1-methylestrone, but gave no details as to yield, analysis etc..

Anal. Calc'd for $C_{19}H_{26}O_2$: C, 80.24; H, 8.51.

Found: C, 80.29; H, 8.66.

(b) *With p-toluenesulfonic acid.* This catalyst has already been found useful in a similar rearrangement in the chrysene series (7). One-hundred milligrams of IX in 5 cc. of acetic anhydride was warmed for four and one-half hours on the steam-bath with 30 mg. of p-toluenesulfonic acid and then worked up as in (a), yielding 80 mg. (80%) of 1-methylestrone with m.p. 231–240°. One recrystallization sufficed to give pure material. When carried out at room temperature, the yield was reduced to 60 mg. of inferior product (m.p. 217–229°, $[\alpha]_D^{25} + 233^\circ$).

1-Methylestrone methyl ether (Vb). The methylation was carried out in alcoholic solution as described for similar compounds (2,15) and the methyl ether was recrystallized from hexane; m.p. 117–118°, $[\alpha]_D^{25} + 297^\circ$. As was to be expected the absorption spectrum was very similar to that of 1-methylestrone.

Anal. Calc'd for $C_{20}H_{28}O_2$: C, 80.49; H, 8.78

Found: C, 80.63; H, 8.86.

Reduction of 1-methylestrone (Va) to 1-methylestradiol (I). A solution of 0.5 g. of the ketone Va in 100 cc. of anhydrous ether was added over a period of ten minutes to a previously prepared solution (20) of excess lithium aluminum hydride (0.7–0.8 g.) in 40 cc. of ether, and the mixture was warmed for a few minutes. After decomposition with water and addition of acid, the ether layer was separated, washed, dried and evaporated, yielding 0.5 g. of crude material of m.p. 226–230°. Recrystallization from a mixture of hexane and acetone gave 0.44 g. (88%) of 1-methylestradiol with m.p. 233–236°, undepressed on admixture with an authentic specimen (3).

SUMMARY

1. The dibromination of androstane-3,17-dione has been shown to proceed through a 2,2-dibromo derivative VII to the 2,4 isomer VIII. A number of transformations involving these dibromo ketones are described and a satisfactory preparative method for 1,4-androstadiene-3,17-dione is given.

2. In contrast to the usual dienone-phenol rearrangements of steroid dienones in acetic anhydride-sulfuric acid solution, it was noted that such treatment results in considerable sulfonation (evidently at C-16) when applied to 1,4-androstadiene-3,17-dione.

3. The preparation of 1-methylestrone (by a modified dienone-phenol rearrangement) and of 5-methyldioisynolic acid is described. These compounds are inactive estrogenically and the significance of these findings is discussed briefly.

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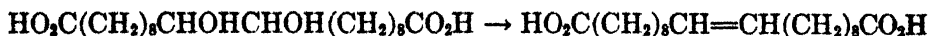
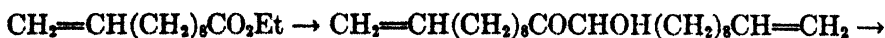
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THE PREPARATION OF 8-OCTADECENEDIOIC ACID

HENRYK SILBERMAN AND SOFIA SILBERMAN-MARTYNCEWA

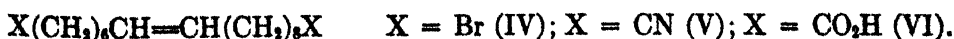
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Long-chain unsaturated α,ω -dicarboxylic acids are convenient intermediates for the preparation of macrocyclic ketones of the civetone type. Ruzicka, Plattner, and Widmer (1) were the first to describe the preparation of *cis*- and *trans*-10-eicosenedioic acid and *cis*- and *trans*-9-octadecenedioic acid. Their method consists of doubling a suitably chosen unsaturated ester molecule, as for example ethyl 10-hendecenoate, by means of the acyloin condensation. This reaction is followed by ozonization of the double bonds at the ends of the molecule and elimination of the hydroxyl groups in the center. The transformations are illustrated by the following equations:



At about the same time Mitter and Bhattacharyya (2) proposed the use of aleuritic acid, 9,10,16-trihydroxyhexadecanoic acid, for the preparation of unsaturated α,ω -dicarboxylic acids. They recommend the treatment of aleuritic acid or its ethyl ester with phosphorus diiodide, thereby replacing the adjacent hydroxyl groups by a double bond and the third hydroxyl by iodine. This method, however, gives poor yields. Three grams of ethyl 16-iodo-9-hexadecenoate was obtained from 20 g. of the ethyl ester, and the product from free aleuritic acid was obtained only in impure form. Mitter and Bhattacharyya reported unusual difficulties in the further reaction of the ester with sodiomalonic ester or potassium cyanide.

In the present paper we describe some transformations of aleuritic acid which proceed smoothly to form the unsaturated, α,ω -dicarboxylic acids in very good yields. Our procedure consists of reducing the ethyl ester of aleuritic acid (I) to the corresponding alcohol (II), replacing the four hydroxyl groups with bromine (III), and removing the vicinal bromine atoms with zinc dust. The 1,16-dibromo-7-hexadecene so formed (IV) reacts smoothly with potassium cyanide under the usual conditions, and the unsaturated dinitrile (V) can be saponified to 8-octadecenedioic acid (VI).



As it was of special interest to ascertain the sterical homogeneity of the unsaturated compounds, considerable effort was devoted to the purification of the 1,16-dibromo compound and the corresponding dioic acid. After purification by high-vacuum distillation, the dibromoalkene showed the expected analytical composition and melted at 16.5–17.5°. This material was repeatedly crystallized from absolute ethanol and petroleum ether (b.p. 45–60°) to give in approximately 40% yield a product with the constant melting point 24.5–25.5° and an unchanged analytical composition. We were unable to isolate a second compound from the mother liquors. The fractions obtained all had melting points ranging between 16.5° and 24.5°. In another attempt, 8-octadecendioic acid was prepared without any purification of the intermediate products. Purification of the end product gave in over 85% yield a compound melting at 110.5–111°, which was not altered by further treatment. We are therefore inclined to assume that the different transformations starting with aleuritic acid yield a sterically homogeneous material. This conclusion is supported by the previous findings of Ruzicka, Plattner, and Widmer (1) that in the reduction of their acyloin compounds two stereoisomeric (*meso* and racemic) dihydroxy derivatives are formed, which lead in sequence to the two unsaturated (*cis* and *trans*) acids in sterically homogeneous form.

An interesting observation was made regarding 1,7,8,16-tetrahydroxyhexadecanealeurityl alcohol. This compound was analyzed and described by Mitter and Mukherjee (3), who reported the melting point 56°. Starting with aleuritic acid melting at 100–101°, in agreement with these authors, we obtained the tetrahydric alcohol melting at the constant temperature 90–90.5° to a cloudy liquid, with meniscus, which clears sharply at 95°. (We presume the formation of liquid crystals.) We are at present unable to explain this divergence, since the high-melting product was the only one obtained by us in oft-repeated reductions and no other material was present in the mother liquors.

EXPERIMENTAL PART

For all melting points and analyses, the materials were dried over P_2O_5 at 60° and 1–2 mm. pressure. The melting points are uncorrected.

1,7,8,16-Tetrahydroxyhexadecane (II). Uniformly high yields were obtained by the modified Bouveault-Blanc procedure described below. In conformity with the experiences of Chuit (4) and Ziegler (5), satisfactory results required the painstaking exclusion of all traces of water, but contrary to the recommendation of Ziegler, addition of the sodium to the boiling ester solution rather than the reverse procedure gave better results in our hands.

Forty grams of the ethyl ester of aleuritic acid, melting at 59–59.5°, [Mitter and Bhat-tacharyya (2), m.p. 50–55°], dried over P_2O_5 at 70° *in vacuo*, was dissolved in 500 ml. of absolute 1-butanol (dried with magnesium), and heated to boiling. Thirty-five grams of metallic sodium cut in large lumps was introduced in two to three lots. After the violent reaction had subsided the mixture was heated in an oil-bath at 150–160° for a further 2½ hours. The contents of the flask were cooled to approximately 70°, decomposed with water, and heated for one-half hour. The warm alcohol layer was separated, washed with warm water, and steam distilled to remove solvent. The remaining yellowish oil solidified on cooling to room temperature. After being filtered and washed, the already pure material was recrystallized from dilute alcohol and benzene. As mentioned above, it showed a constant double transition point: at 90–90.5° it melted to a cloudy liquid, with a meniscus, which turned clear at 95° (sharp); yield 80–85%.

Anal. Calc'd for $C_{18}H_{34}O_4$: C, 66.2; H, 11.7.

Found: C, 65.9, 66.0; H, 11.7, 11.6.

1,7,8,16-Tetrabromoheptadecane (III). Thirty grams of the tetrahydroxy compound was treated with 300 ml. of a solution of HBr in glacial acetic acid (sp. gr. 1.25 = 22.5% HBr by wt.). On gentle warming in an oil-bath the solid disappeared into the solution. The bath was brought slowly (two hours) to 80–85° and kept for two hours at 85–95° and for four hours at 100–105°. After cooling to approximately 40°, the excess HBr and acetic acid were removed under reduced pressure. The oily, dark-brown residue was taken up with ether and the ethereal solution washed with water and bicarbonate solution. The dried ethereal solution was repeatedly decolorized with charcoal and the ether was removed. A pale yellow, heavy oil remained which turned to a waxy, non-crystalline solid on cooling to –10°. The yield (55 g.) was almost quantitative. The bromine content was found to be 58.53% whereas $C_{18}H_{30}Br_4$ requires 58.95% Br.

In an attempt to purify the crude material, 2 g. was subjected to a short-path distillation at 0.01 mm. and an oil-bath temperature of 180–200°. The resulting pale yellow oil had the same physical properties and the bromine content was found to be 58.6%.

1,16-Dibromo-7-hexadecene (IV). For the debromination of the tetrabromide, 32 g. of zinc powder was activated under 100 ml. of 98% alcohol by boiling 3–5 minutes with 1 ml. of concentrated hydrogen bromide solution. The mixture was cooled to room temperature and a solution of 52 g. of the crude tetrabromide in 70 ml. of benzene was added in three to four portions with constant shaking. The temperature rose with each addition and was kept near the boiling point for approximately 15 minutes with constant mixing. The boiling solution was filtered from the excess zinc powder and the filtrate was washed with water, dilute sulfuric acid, and bicarbonate solution. After drying over Na_2SO_4 , the solvent was removed under reduced pressure. The remaining oil, which melted at 16–17°, could be purified by high-vacuum distillation, but crystallization was more convenient. The material was dissolved at 35–40° in 5–6 times its weight of 98% alcohol and filtered from a small insoluble residue. The filtrate, which should remain clear at 25–30°, was cooled slowly to –10°, the dibromo compound separating in the form of beautiful silky needles which turned the solution into a solid paste. After standing 12 hours in a refrigerator the crystalline precipitate was filtered through a cooled Büchner funnel and washed with small portions of cold alcohol. The melting point of the purified material after repeated crystallizations from alcohol, petroleum ether, and acetone was constant at 25–25.5°.

Anal. Calc'd for $C_{16}H_{30}Br_2$: C, 50.25; H, 7.9; Br, 41.8.

Found: C, 50.6; H, 8.0; Br, 42.0.

A material purified by distillation only, melted at 16.5–17.5° and contained 42.1% bromine.

8-Octadecenedinitrile (V). To 25 g. of 1,16-dibromo-7-hexadecene in 150 ml. of alcohol was added a solution of 14 g. of potassium cyanide and 0.75 g. of potassium iodide in 30 ml. of water. This mixture was boiled 15 hours under reflux with good stirring. An additional 7 g. of potassium cyanide in 15 ml. of water was added and refluxing was continued for 15–20 hours. After cooling, the reaction mixture was taken up in water and ether. The ethereal solution was washed with bicarbonate solution and water and dried with sodium sulfate. After removal of the solvent, the sludge of pale yellow crystals which remained was purified by high-vacuum distillation. After a small forerun the main fraction distilled at 182–185°/0.5 mm. The distillate solidified to a sludge of white waxy crystals which sintered at 35–38° and melted at 45–47°; yield 85–90%.

A material free of all traces of halogen and distilling with a very small forerun can be obtained if after the first reaction period with potassium cyanide the crude dinitrile is separated by partition between ether and water, freed from solvent, and treated in a water-alcohol solution with a fresh portion of 10 g. of potassium cyanide and 0.75 g. of potassium iodide.

Anal. Calc'd for $C_{18}H_{30}N_2$: C, 78.8; H, 11.0; N, 10.2.

Found: C, 78.5; H, 11.3; N, 9.8.

8-Octadecenedioic acid (VI). The 8-octadecenedinitrile was saponified by dissolving 2.5

g. in 20 ml. of alcohol, adding 4 g. of potassium hydroxide dissolved in 10 ml. of water, and refluxing the homogeneous solution strongly for 30 hours. The alcohol was removed by evaporation and replaced with water, and the hot alkaline solution was filtered from impurities. Upon acidification of the filtrate there was obtained a white fluffy precipitate of the crude acid melting at 102–106°; yield 2.55 g. (90%). After repeated crystallization from dilute alcohol and benzene the material attained the constant melting point 110.5–111°.

Anal. Calc'd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.34; Eq. wt., 156.2.

Found: C, 69.0; H, 10.5; Eq. wt., 156, 156.2.

Dimethyl 8-octadecenedioate. The ester was prepared by boiling 0.3 g. of the acid for 3 hours with 4 ml. of methanol and a trace of sulfuric acid. After the usual purification, a solid material was obtained which after rubbing with a few drops of ice-cold petroleum ether and recrystallization from 90% methanol sintered at 32° and melted at 36–37°.

Anal. Calc'd for $C_{20}H_{38}O_4$: C, 70.5; H, 10.6.

Found: C, 70.6; H, 10.7.

Octadecanedioic acid. For the purpose of further characterization, the unsaturated acid was hydrogenated to the saturated compound, whose properties have been described by Chuit (4). A sample (0.6 g.) of the acid recrystallized from thiophene-free benzene was hydrogenated in 15 ml. of purified alcohol with 0.25 g. of palladium charcoal (6). The calculated amount of hydrogen (55 ml.) was taken up in the course of half an hour. After separation from the catalyst, the filtrate was saponified by heating two hours on a water-bath with 10 ml. of 2 *N* sodium hydroxide solution. The alcohol was removed by evaporation and the acid precipitated with dilute hydrochloric acid. The crude octadecanedioic acid showed the expected melting point 124.5°, which after repeated recrystallization from benzene remained at 124.5–125°.

Anal. Calc'd for $C_{18}H_{34}O_4$: Eq. wt., 157.2.

Found: Eq. wt., 156.2, 157.

The yield was nearly quantitative.

SYDNEY, AUSTRALIA

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COMPLEX METAL ALKYL

DALLAS T. HURD

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The coordination of negative ions to acceptor atoms to form complex anions is an old and well-established phenomenon. More common examples of compounds formed in this fashion include the fluoborates, fluosilicates, and chloroaluminates.

The first example of complex anion formation involving exclusively alkyl groups bonded to the central atom was realized by Schlesinger and Brown (1) in the synthesis of $\text{LiB}(\text{C}_2\text{H}_5)_4$ although the possibility of forming compounds of the type MBR_4 (where R represents an alkyl or aryl group) was recognized earlier (2). Several examples of complex formation between the alkyls of electropositive metals and zinc alkyls are mentioned in the literature but these were not considered by the investigators as involving complex anions.

This paper describes the preparation and some properties of three additional complex alkyl compounds of this type: $\text{LiAl}(\text{CH}_3)_4$, $\text{Li}_2\text{Zn}(\text{CH}_3)_4$, and $\text{LiB}(\text{CH}_3)_4$.

EXPERIMENTAL

All preparations were carried out in nitrogen atmospheres and all material transfer was performed in a nitrogen-filled dry box.

$\text{LiAl}(\text{CH}_3)_4$. Aluminum trimethyl was prepared by adding 22 g. of anhydrous aluminum chloride dissolved in 250 ml. of dry ether to the methylmagnesium bromide prepared from 20 g. of magnesium. After 2 hours' reflux, the excess ether was distilled off, then at 60° the aluminum trimethyl etherate was distilled from the magnesium halide on a vacuum chain. This material was transferred to a flask containing a filtered ether solution of the lithium methyl prepared from 1 g. of lithium with methyl chloride. (This represented an 85% excess of aluminum trimethyl assuming a 100% yield in both preparations.) It was observed that some heat was liberated in the process of mixing. The resulting ether solution was evaporated to remove the ether, then was heated in a vacuum system at 80° until the pressure was below 50 microns. There remained a quantity of white solid $\text{LiAl}(\text{CH}_3)_4$.

This compound may be stable in very dry air although in the usual laboratory atmosphere it became warm and ignited spontaneously after a few minutes exposure. The dry salt is very soluble in ether and will adsorb ether vapor rapidly. If the dry salt is added to water or alcohol, a violent reaction occurs with inflammation and the reacting solid is heated to incandescence. If the ether solution of the compound is poured into water, a large evolution of methane ensues together with a white precipitate of aluminum hydroxide. The ether solution reacts rapidly with silicon tetrachloride to effect methylation.

The compound was analyzed by dissolving a weighed sample in ether, then adding this solution to dilute HCl to decompose the complex and form the chlorides of aluminum and lithium. Aluminum was precipitated as $\text{Al}(\text{OH})_3$, ignited, and weighed as Al_2O_3 . Lithium was separated and weighed as Li_2SO_4 .

Anal. Calc'd for $\text{LiAl}(\text{CH}_3)_4$: Li, 7.4; Al, 28.69.

Found: Li, 7.3, Al, 28.85.

$\text{Li}_2\text{Zn}(\text{CH}_3)_4$. Zinc dimethyl was prepared by adding 27 g. of anhydrous zinc chloride in ether to the methylmagnesium bromide prepared from 5.5 g. of magnesium. This was

followed by reflux for an hour and finally by distillation of the ether and the volatile product in a vacuum system into a storage bulb. To this solution of zinc dimethyl was added the filtered ether solution of lithium methyl prepared from 1.5 g. of lithium with methyl chloride. A portion of the resulting mixture was evaporated on the vacuum chain and pumped at room temperature to remove ether and excess zinc methyl. The solid that remained was analyzed for lithium and zinc by dissolving in dilute acid, separation of the zinc as ZnS, and determination as $\text{Zn}(\text{NH}_4)\text{PO}_4$. Lithium was determined as Li_2SO_4 .

Anal. Calc'd for $\text{Li}_2\text{Zn}(\text{CH}_3)_4 \cdot \text{C}_2\text{H}_5\text{O}$: Li, 6.51; Zn, 30.7.

Found: Li, 6.43; Zn, 31.4.

Since the ratio of Li to Zn was almost two to one, and tests for chloride in the water solution of the compound were negative, it was considered that a very stable etherate was present. (Many alkyls, particularly those of acceptor atoms, are noted for the formation of very stable etherates. In some cases a physical separation of the alkyl from the ether is extremely difficult or may even be impossible.) Heating under vacuum to 60° did not materially alter the analyses.

$\text{Li}_2\text{Zn}(\text{CH}_3)_4 \cdot \text{C}_2\text{H}_5\text{O}$ did not catch fire upon exposure to air although it did pick up moisture rapidly, obviously with decomposition and the evolution of gas. If a small amount was ignited on a spatula, it burned readily. The solid reacted with water with considerable violence and the evolution of gas, but no inflammation, to produce a strongly alkaline solution and a flocculent white precipitate. This solution showed no reducing properties.

$\text{LiB}(\text{CH}_3)_4$. Boron trimethyl was prepared by adding 25 g. of boron fluoride etherate to the methylmagnesium bromide solution formed from 12.5 g. of magnesium. The reaction mixture was distilled and the boron methyl, together with some ether, was collected in a trap cooled with Dry Ice. This solution was added cold to the clear filtered ether solution of lithium methyl prepared from 1 g. of lithium with methyl chloride. The resulting mixture was evaporated under vacuum and the ether, together with excess boron trimethyl, was removed to leave a crystalline white solid. This solid was heated *in vacuo* at 60° for several hours, then was analyzed.

Anal. Calc'd for $\text{LiB}(\text{CH}_3)_4$: Li, 8.95; Found: Li, 9.68.

Lithium was determined as Li_2SO_4 . Analysis for boron on complex organoboron compounds was attempted by fusion with Na_2O_2 followed by potentiometric titration but this was found to be a very unsatisfactory procedure. The main difficulty appeared to be getting complete removal of the organic groups from the boron by the oxidation procedure. Tests for halogen in this compound were negative.

$\text{LiB}(\text{CH}_3)_4$ appears to be stable in very dry air, although in moist air it was observed occasionally to ignite spontaneously. The solid is quite soluble in ether, and, if a relatively large amount of water is added rapidly to the dry salt, it dissolves quickly with no apparent reaction to form a highly alkaline solution with strong reducing properties, i.e. decolorizes KMnO_4 solution rapidly. Placing a drop of water on a small pile of the solid usually caused ignition. Acidification of the water solution of $\text{LiB}(\text{CH}_3)_4$ released large volumes of spontaneously inflammable gas having the characteristic odor of boron trimethyl. Addition of hydrogen peroxide to the solution produced a slow evolution of gas bubbles as did methanol. Ethanol and acetone produced no gas evolution. The amount of gas released upon acidification of the water solution decreased if the solution was allowed to stand exposed to air, and after a few hours, the gas evolved was no longer spontaneously inflammable.

The water solution was found to be conducting, and a fresh sample was electrolyzed in a small electrolysis apparatus. About half again as much gas was evolved at the anode as at the cathode. This gas was not spontaneously inflammable. It was analyzed on the mass spectrometer, and its principal components were identified tentatively as methane, ethane, and cyclopropane.

DISCUSSION

The formation of a complex ion by coordination of a methyl group to an acceptor atom presumably involves a transfer of a *negative* methyl ion, i.e., a

methyl group carrying an unshared electron pair. This behavior is not unexpected since the physical characteristics of alkali metal methyls suggests a certain degree of ionic character for the alkyl group in these compounds. Indeed, methyl groups (in addition to hydrogen atoms) are rather unique in that they can take part in various reactions as positive ions, free radicals, or negative ions, to form stable compounds. This behavior is shown to a lesser degree by ethyl groups, and the degree of electronegative character decreases as the size of the straight chain aliphatic group increases.

Many other groups, such as alkoxyl, hydroxyl, hydride ion, halide ion, etc., coordinate to acceptor atoms to form complex ions, and a large number of mixed compounds must be possible. For example, Finholt, Bond, and Schlesinger have indicated the formation of $\text{LiAlH}_2(\text{CH}_3)_2$ (3).

Complex alkyls, such as those described here, may be of considerable interest in studying relative reactivities of various organic groups. It is possible that some, such as $\text{LiAl}(\text{CH}_3)_4$, may be useful as alkylating agents in special syntheses.

SCHENECTADY, NEW YORK

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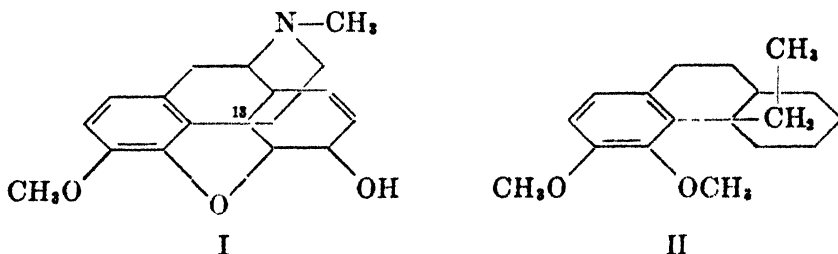
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STRUCTURE STUDIES IN MORPHINE. THE DEGRADATION OF DIHYDROCODEINE TO NITROGEN-FREE COMPOUNDS

HENRY RAPOPORT

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The formula for morphine and its methyl ether, codeine (I), accepted at present¹ as best explaining the many and complicated facts of morphine chemistry (3) is that of Gulland and Robinson (4). However, an important point still without direct experimental proof is the juncture of the ethanamine chain at carbon 13.² It is the objective of this work ultimately to provide evidence on this question by degrading codeine to 13-ethyloctahydrodimethylmorphol (II)³ by a series of reactions which would cause no rearrangements in the fundamental skeleton of the molecule. This degradation product, containing only two asymmetric carbon atoms, might be amenable to an unambiguous synthesis and thus supply an absolute proof of structure. At present, we are reporting some preliminary degradative results.



Degradation of codeine itself has invariably led to ejection or migration of the ethanamine chain and completely aromatic phenanthrene derivatives (3, 5). However, in derivatives where aromatization has been blocked by prior hydrogenation of the alicyclic double bond, degradation has proceeded to nitrogen-free compounds without loss of the two-carbon chain (6), but as yet compound II has not been realized.

Because of the above considerations, dihydrocodeine (IV), which has the hydrogenated structure necessary for retention of the ethanamine chain, was selected as starting material for the degradation. Previous attempts to obtain a nitrogen-free compound from dihydrocodeine have usually resulted in unidentified oils (7, 8). In only one case (9) was a crystalline substance isolated (in very

¹ Some of the recent data on the phenyldihydrothebaines (1) that seem inexplicable on the basis of the present formula have been interpreted by Robinson in a preliminary note (2) by assuming a fundamental rearrangement in the morphine skeleton.

² The most direct experimental evidence supporting juncture at carbon 13 has been presented by Schöpf, *Ann.*, **452**, 211 (1927); however, this work still does not supply the unqualified proof desired.

³ For consistency with previous work, the nomenclature of morphine chemistry is retained throughout.

low yield), and we shall show subsequently that the structure assigned to this product is probably incorrect. It is difficult to perceive why the degradation of dihydrocodeine should give such indeterminate results if the assigned structure (IV) is correct; therefore, these reactions and products were re-examined in detail.

Dihydrocodeine was converted to dihydro- α -methylmorphimethine (Δ -9,10) (V) in almost quantitative yield, and the methine degraded by refluxing its methohydroxide with alkali according to Speyer and Krauss (9). In contrast to their results, the only product was a small amount of an intractable red solid. However, when the methohydroxide, prepared from the methiodide and silver oxide, was dry distilled in vacuum, considerable oily distillate was obtained that could be separated into a basic fraction, 34% of the original calculated as recovered methine, and a neutral fraction corresponding to 59% of the original. After all attempts to crystallize this neutral fraction failed, recourse was made to the possible preparation of crystalline derivatives.

By esterifying the neutral fraction with *p*-phenylbenzoyl chloride in pyridine, it could be separated by vacuum distillation into a relatively volatile non-alcoholic fraction (40 to 50%) and the residual *p*-phenylbenzoate of the alcoholic portion. Analysis of the purified, oily non-alcoholic fraction showed it had the composition $C_{18}H_{20}O_2$, which was a carbon and two hydrogens more than expected. It was non-phenolic, contained two methoxyl groups (Zeisel), absorbed two moles of hydrogen, and was recovered unchanged from attempts to prepare ketone derivatives. On the basis of these reactions, it was assigned the structure 6-methoxy-13-vinylhexahydromethylmorphenol (Δ -9,10) (VIII). This assigned structure was confirmed by the identity of its crystalline hydrogenation product with the 6-methoxy-13-ethyloctahydromethylmorphenol (XII) prepared by degradation of codeine methyl ether (XIII).

The surprising discovery in the neutral fraction of material with the 6-hydroxyl group methylated indicated that the recovered methine might also be partially etherified. Therefore, the basic fraction was converted to methiodide, which after repeated crystallization melted over a wide range and appreciably lower than the methiodide of the original methine, possibly due to the presence of both 6-hydroxy and 6-methoxy methines in the recovered material.

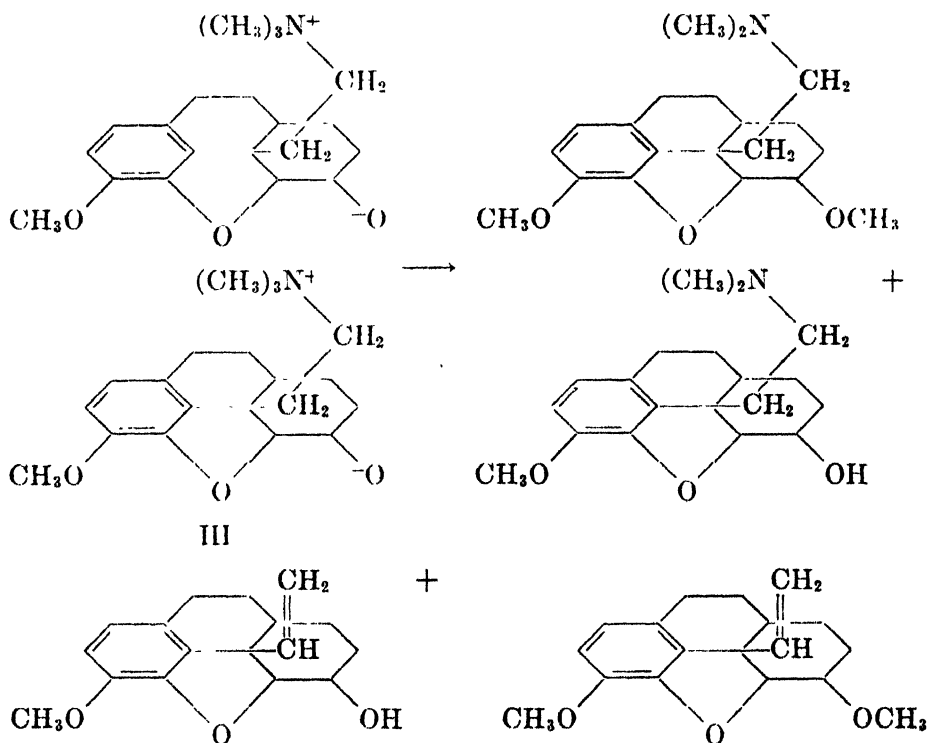
The alcoholic fraction of the neutral, degraded material was isolated in 81% yield as the crystalline *p*-phenylbenzoate and saponification gave the free alcohol, m.p. 102–103°, which was non-phenolic and absorbed 2 moles of hydrogen. This alcohol, to which the structure 6-hydroxy-13-vinylhexahydromethylmorphenol (Δ -9,10) (VII) is assigned, has been previously reported (9) as melting at 115°. However, the above evidence and the fact that the earlier workers obtained their compound crystalline only after several months standing in aqueous ethanol and in extremely low yield makes structure VII very improbable for the higher-melting material.

In order to establish the structure of these degradation products as securely as possible, tetrahydro- α -methylmorphimethine (VI) was subjected to a similar degradation and found to give identical results. Also, to eliminate any possible

cyclization reactions involving the hydroxyl group and the double bonds, the crude degraded material was purified both before and after hydrogenating. In every case, 6-hydroxy-13-ethyloctahydromethylmorphenol (XI) and the 6-methoxy analog (XII) were obtained as the end products and in good yield. Both the dihydromethine (V) and the tetrahydro methine (VI) gave recovered basic material whose methiodides melted over a wide range, possibly due to the presence of both 6-hydroxy and 6-methoxy methines. The composition of these fractions is being examined further and will be reported at a later date.

The presence among the degradation products of morphine alkaloids of compounds in which the alcoholic hydroxyl has been methylated during the degradative procedure has heretofore been unreported, and it is interesting to consider how such compounds might have originated. Any explanation must take into account the fact that the hydroxyl group in the parent substance, dihydrocodeine (IV), is indifferent to methylation by the Rodionov procedure (10). It must also explain why degradation of tetrahydro- α -methylmorphimethine (VI) gives 40 to 50% of recovered methine whereas from the 6-methoxy analog (XV) only 2 to 3% of undegraded material is obtained.

The above observations might indicate the existence of an intermediate in the degradation of the 6-hydroxy compound which makes the hydroxyl group more susceptible to etherification and influences the course of the degradation to give a higher proportion of undegraded material. A possible intermediate that fulfills these requirements is the inter-molecular salt (III), which on dry distillation could theoretically give all four products, shown below.



Work is continuing on the mechanism of the degradation with compounds containing the 6-hydroxyl group, and also on the conversion of 6-hydroxy-13-ethyloctahydromethylmorphenol (XI) to 13-ethyloctahydrodimethylmorphol (II).

We are indebted to Mallinckrodt Chemical Works, St. Louis, Mo., for the generous gift of codeine used in this research.

EXPERIMENTAL

All melting points are corrected, and all above 200° were taken in evacuated tubes; rotations are in 95% ethanol unless otherwise stated. Microanalyses were performed by C. W. Koeh and V. H. Tashinian.

Dihydrocodeine (IV) Dihydrocodeine was prepared by a modification of the method of Wieland and Koralek (8). A solution of 50 g. (0.158 mole) of codeine ($\cdot\text{H}_2\text{O}$) in 175 ml. of methanol containing 2.5 g. of 10% palladium on barium sulfate was hydrogenated at room temperature and thirty pounds pressure. After two hours, hydrogenation ceased with the absorption of 1.04 moles of hydrogen. Filter-aid was added, the solution filtered, and the filtrate concentrated on the steam-bath to a syrupy residue which gave 50 g. (94%) of dihydrocodeine ($\cdot 2\text{H}_2\text{O}$), m.p. 53–55° (11), on addition of 100 ml. of water and cooling. This dihydrate, when heated at 75° and 0.1 mm. pressure gave a crystalline sublimate of the anhydrous form, m.p. 112°, $[\alpha]_D^{20} -145^\circ$ (ethanol, $c = 1.38$).

The *methiodide* was prepared in quantitative yield directly from the dihydrate in 95% ethanol and, after drying in a vacuum at 125° overnight, melted at 258–260° (8).

Dihydro- α -methylmorphimethine (Δ -9,10) (V) To a solution of 65 g. (0.147 mole) of dihydrocodeine methiodide in 200 ml. of water was added 200 ml. of a 30% potassium hydroxide solution and the mixture refluxed for 30 minutes. After cooling, the oily layer was removed by extraction with one 250-ml. portion and three 125-ml. portions of ether, the combined ether extracts were dried over potassium carbonate, filtered, and the ether evaporated on the steam-bath. The residual oily methine was converted directly to the *methiodide* by dissolving in 200 ml. of ethanol and warming on the steam-bath with methyl iodide. One recrystallization from ethanol gave 63.2 g., 91%, of the monohydrate, m.p. 154–156° with loss of solvent. Drying in a vacuum at 125° overnight gave the anhydrous form, m.p. 224–226° (12).

Tetrahydro- α -methylmorphimethine (VI). The dihydro- α -methylmorphimethine obtained from the degradation of 59.4 g. (0.134 mole) of dihydrocodeine methiodide was hydrogenated in the manner described previously for the reduction of codeine. After three hours, hydrogenation ceased with a total absorption of 1.02 moles of hydrogen. The residue after evaporation of the methanol was converted to the *methiodide* by warming in 150 ml. of ethanol with methyl iodide. One recrystallization from ethanol and drying in a vacuum at 125° overnight gave 57.2 g., 93% based on dihydrocodeine methiodide, of the anhydrous methiodide, m.p. 225–227° (7).

Degradation of dihydro- α -methylmorphimethine (Δ -9,10) (V). A. By the method of Speyer and Krauss (9). Degradation of dihydro- α -methylmorphimethine (Δ -9,10) methiodide as directed by Speyer and Krauss (9) gave only a dark brown solid which failed to crystallize from aqueous ethanol even after months of standing. None of the material they reported melting at 115° could be obtained.

B. By dry distillation of the methohydroxide. Silver oxide was freshly prepared by adding 125 ml. of 3 N sodium hydroxide to a solution of 34.0 g. (0.20 mole) of silver nitrate in 125 ml. of water. The precipitate was washed with water until the washings were neutral and then with a portion of water previously boiled to remove carbon dioxide. From this point on, precaution was taken to exclude carbon dioxide from the reaction mixture. Using 150 ml. of water to effect the transfer, the silver oxide thus prepared was added to a warm solution of 22.85 g. (0.050 mole) of dihydro- α -methylmorphimethine methiodide in 350 ml. of water and the mixture was shaken at room temperature for 8 hours. Filter-aid was then

p-phenylbenzoyl chloride and then allowed to stand at room temperature overnight. The pyridine was removed by distillation at the water-pump and the residual magma was heated on the steam-bath with 80 ml. of 0.5 *N* K_2CO_3 for 20 minutes, after which 125 ml. of benzene was added. Using warm solutions to prevent emulsion formation, the benzene layer was washed with four 40-ml. portions of 0.5 *N* K_2CO_3 and two 40-ml. portions of water, and each wash portion was in turn extracted with two 40-ml. portions of benzene. After drying over K_2CO_3 , the combined benzene solutions were evaporated on the steam-bath and the residue distilled for 15 hours at 135°/0.1 mm. in a modified molecular distillation apparatus to give 3.96 g., 50% of the original, as a colorless, oily distillate. A sample of this material, 6-methoxy-13-vinylhexahydromethylmorphenol (Δ -9,10) (VIII), was redistilled at 100°/0.05 mm. It is a fairly mobile oil with $[\alpha]_D^{25} +61.0^\circ$ (ethanol, $c = 1.532$); $n_D^{25} 1.5861$.

Anal. Calc'd for $C_{18}H_{26}O_4$: C, 76.02; H, 7.09.

Found: C, 75.92; H, 7.05.

A sample of this compound, hydrogenated in methanol with a platinum oxide catalyst, absorbed 1.9 moles of hydrogen in 15 minutes, after which hydrogenation ceased. Evaporation of the solvent gave the crystalline tetrahydro derivative (XII) described below.

The residue from the 15-hour distillation was taken up in 150 ml. of ethanol and, after decolorizing with carbon, gave 4.66 g. of crystalline material on cooling. Concentration of the mother liquor to about 30 ml. gave an additional 0.73 g.; total 5.39 g., m.p. 165–170°, 81% yield of 6-hydroxy-13-vinylhexahydromethylmorphenol (Δ -9,10) *p*-phenylbenzoate, based on the nonrecovered fraction. Several crystallizations from ethanol gave material melting at 173–174° which very slowly sublimed at 160°/0.05 mm., $[\alpha]_D^{25} +73.4^\circ$ (dioxane, $c = 0.92$).

Anal. Calc'd for $C_{20}H_{28}O_4$: C, 79.98; H, 5.82.

Found: C, 79.70; H, 5.73.

The ester was saponified by adding 200 ml. of 5 *N* ethanolic KOH to a solution of 8.9 g. (0.02 mole) of ester in 200 ml. of ethanol and refluxing in a nitrogen atmosphere for 3 hours. After cooling, the solution was filtered from the precipitated potassium *p*-phenylbenzoate and the filtrate concentrated at reduced pressure. Water was added, the concentration repeated, and 100 ml. of water added to the residue followed by extraction with one 100-ml. portion and two 50-ml. portions of ether. After washing with water and drying over Na_2SO_4 , the combined ether extracts were evaporated on the steam-bath to give a slightly yellow residue which crystallized on cooling; yield 5.12 g., 96%, of material melting at 97–101°. Several crystallizations from hexane and a sublimation at 80°/0.05 mm. gave a sample of 6-hydroxy-13-vinylhexahydromethylmorphenol (Δ -9,10) (VII) that had m.p. 102–103° and $[\alpha]_D^{25} +77.1^\circ$ (ethanol, $c = 1.012$).

Anal. Calc'd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71.

Found: C, 75.43; H, 6.58.

Hydrogenation of this compound in methanol with a platinum oxide catalyst ceased after the absorption of 2 moles of hydrogen in 30 minutes and gave the tetrahydro derivative (XI) described below.

2. *Separation of neutral material into alcoholic and non-alcoholic fractions after hydrogenation.* Crude neutral degraded material, 7.5 g. (0.028 mole, assuming all alcohol, VII), was dissolved in 40 ml. of methanol and hydrogenated using 0.75 g. of 10% palladium on barium sulfate as catalyst. After the absorption of 1.7 moles of hydrogen in 3 hours, hydrogenation ceased, and evaporation of the methanol left 7.42 g. of hydrogenated material. This was esterified with *p*-phenylbenzoyl chloride exactly as described above and sublimation of the esterification reaction product at 125°/0.3 mm. for 15 hours gave 2.2 g., 30%, of a waxy, crystalline sublimate, m.p. 45–49°. In preliminary experiments to determine the structure of this compound, it was recovered quantitatively and unchanged from attempted oxime and semicarbazone formation. Its structure was established as 6-methoxy-13-ethyloctahydromethylmorphenol (XII) by its identity with the compound prepared from codeine methyl ether as described below. Purification with considerable loss was effected by several crystallizations from pentane in which it is quite soluble even cold, and a final sublimation at 40°/0.05 mm. gave material of m.p. 51–52°, $[\alpha]_D^{25} -44.0^\circ$ (ethanol, $c = 1.376$).

Anal. Calc'd for $C_{18}H_{24}O_4$: C, 74.97; H, 8.39; OCH_3 , 21.5.

Found: C, 74.90; H, 8.35; OCH_3 , 21.1.

The residue from the sublimation of the esterified mixture was dissolved in 200 ml. of ethanol and filtered after treating with carbon. Concentration of the filtrate to 75 ml. and cooling gave 4.9 g. of crystalline material; further concentration of the mother liquor to 20 ml. gave 0.7 g. more; total, 5.6 g., m.p. 167–171°, 65% yield based on unrecovered material. Several crystallizations from ethanol gave pure 6-hydroxy-13-ethyloctahydromethylmorphenol *p*-phenylbenzoate, m.p. 170–172°, $[\alpha]_D^{20} -3.42^\circ$ (dioxane, $c = 1.022$)

Anal. Calc'd for $C_{30}H_{40}O_6$: C, 79.27; H, 6.65.

Found: C, 79.14; H, 6.65.

6-Hydroxy-13-ethyloctahydromethylmorphenol (XI) was obtained in 85% yield by saponification of the pure *p*-phenylbenzoate ester (above) with alcoholic KOH as described previously for the ester of the hexahydro derivative (VIII). It is a viscous, colorless oil that distills rapidly at 100°/0.05 mm. and shows no tendency to crystallize

Degradation of tetrahydro- α -methylmorphimethine (VI). The degradation of tetrahydro- α -methylmorphimethine by dry distillation of its methohydroxide was carried out exactly as described above for the dihydro compound. From 23 g. (0.05 mole) of methiodide there resulted 6.85 g. of basic material, equivalent to a 43% recovery of methine. Conversion to the methiodide and repeated crystallization of the latter from ethanol gave material melting from 220–233°, indicating it was probably a mixture of tetrahydro- α -methylmorphimethine methiodide, m.p. 225–227°, and tetrahydro- α -dimethylmorphimethine methiodide, m.p. 247° (13).

The neutral fraction consisted of a viscous oil, 7.64 g., 56% yield based on total methiodide or 98% allowing for recovered methine. It was separated into alcoholic and non-alcoholic fractions both directly and after hydrogenation, exactly as described above for the degraded material from the dihydro compound (V), and the following products were obtained:

6-Methoxy-13-vinyloctahydromethylmorphenol (IX). Esterification of the neutral degraded material with *p*-phenylbenzoyl chloride and distillation of the reaction mixture under reduced pressure gave the oily 6-methoxy-13-vinyloctahydromethylmorphenol in 36% yield. Hydrogenation in methanol with a 10% palladium on barium sulfate catalyst ceased after the absorption of 1.0 mole of hydrogen in one hour. Evaporation of the methanol and sublimation of the residue resulted in a 96% yield of 6-methoxy-13-ethyloctahydromethylmorphenol as a crystalline sublimate, m.p. 47–49°; after one crystallization from pentane, m.p. 50–52°.

6-Hydroxy-13-vinyloctahydromethylmorphenol (X). The residue from the vacuum distillation of the esterification reaction mixture, on crystallization from ethanol, gave a 76% yield of 6-hydroxy-13-vinyloctahydromethylmorphenol *p*-phenylbenzoate, m.p. 168–170° after several crystallizations from ethanol; $[\alpha]_D^{20} +53.9^\circ$ (dioxane, $c = 0.946$).

Anal. Calc'd for $C_{30}H_{40}O_6$: C, 79.62; H, 6.24.

Found: C, 79.48; H, 6.49.

Saponification of this ester with ethanolic KOH in the manner described above gave a 91% yield of 6-hydroxy-13-vinyloctahydromethylmorphenol as a viscous oil that absorbed 1.02 moles of hydrogen on reduction in methanol with a 10% palladium-barium sulfate catalyst.

Hydrogenation of the crude neutral degraded material (1.0 mole of hydrogen absorbed) and esterification of the reduced mixture with *p*-phenylbenzoyl chloride gave, on separation in the manner described above, a 34% yield of 6-methoxy-13-ethyloctahydromethylmorphenol (XI), m.p. 48–50°, and a 69% yield of 6-hydroxy-13-ethyloctahydromethylmorphenol (XI) as the *p*-phenylbenzoate, m.p. 170–172°.

Preparation of 6-methoxy-13-ethyloctahydromethylmorphenol (XII) from codeine methyl ether (XIII). Codeine methyl ether (XIII). Codeine methyl ether was prepared directly as the methiodide from morphine by the method of Pschorr and Dickhauser (14); m.p. 252–254° (lit. m.p. 257°).

α -Dimethylmorphimethine (XIV). Degradation of codeine methyl ether methiodide by

refluxing with aqueous sodium hydroxide resulted in a 72% yield of α -dimethylmorphimethine, m.p. 92–94° (14).

Tetrahydro- α -dimethylmorphimethine (XV). Hydrogenation of α -dimethylmorphimethine was carried out by the method of Faltis and Suppan (13). The tetrahydro reduction product was converted directly to the *methiodide* in ethanol, 81% yield, m.p. 246–248° (13).

6-Methoxy-13-vinyloctahydromethylmorphenol (IX). Tetrahydro- α -dimethylmorphimethine was degraded by dry distillation of the methiodide exactly as described above. From 15 g. (0.032 mole) of methiodide there was recovered 0.27 g., 2.6%, of methine (methiodide, m.p. 246–248°) and 7.90 g. of oily 6-methoxy-13-vinyloctahydromethylmorphenol, 87% yield based on total methiodide, or 90% allowing for recovered methine.

6-Methoxy-13-ethyloctahydromethylmorphenol (XII). Hydrogenation of 7.90 g. (0.028 mole) of 6-methoxy-13-vinyloctahydromethylmorphenol in 50 ml. of methanol with 0.79 g. of 10% palladium-barium sulfate ceased after 2 hours at room temperature and atmospheric pressure with the absorption of 1.05 moles of hydrogen. The catalyst was removed and the filtrate evaporated to dryness on the steam-bath to give a crystalline residue that was sublimed at 50°/0.1 mm. There was thus obtained 7.52 g., 94%, of 6-methoxy-13-ethyloctahydromethylmorphenol as a crystalline sublimate, m.p. 47–49°. Crystallization from pentane gave material whose m.p. of 51–52° was not depressed on admixture with the neutral, completely hydrogenated, non-alcoholic fraction resulting from the various degradations above, thus establishing the identity of the compounds.

SUMMARY

6-Hydroxy-13-ethyloctahydromethylmorphenol and 6-methoxy-13-ethyloctahydromethylmorphenol have been obtained from the degradation of dihydrocodeine.

The structure of 6-methoxy-13-ethyloctahydromethylmorphenol from dihydrocodeine has been established by its identity with the degradation product from codeine methyl ether.

Degradation of dihydro- and tetrahydro- α -methylmorphimethine has been shown to proceed with partial methylation of the hydroxyl group on carbon six.

BERKELEY, CALIFORNIA

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SOME 2-ACETHYLTHIOPHENE DERIVATIVES AND RELATED ACETOPHENONE ANALOGS

WILLIAM S. EMERSON AND TRACY M. PATRICK, Jr.

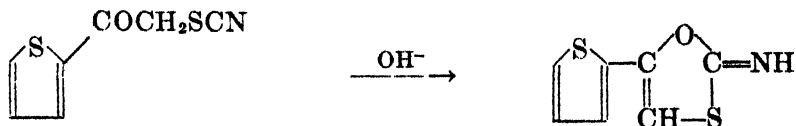
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2-Acetylthiophene has been prepared in 86% yield by treating thiophene with acetic anhydride in the presence of iodine (1), in 79–83% yield from thiophene, acetyl chloride, and stannic chloride (2), and in 75% yield from thiophene, acetyl chloride, and aluminum chloride by the Perrier technique (3). More recently thiophene has been acetylated in yields up to 94% by means of acetic anhydride in the presence of such catalysts as zinc chloride (4), activated clays (5, 6), and inorganic oxyacids (7), and in 45% yield by means of acetic acid and phosphorus pentoxide (8). With 2-chlorothiophene, acetic anhydride, and phosphoric acid, the yield of 2-acetyl-5-chlorothiophene was 70% (7). Starting with 2-chlorothiophene we have prepared 2-acetyl-5-chlorothiophene in 71% conversion and 84% yield by the acetic anhydride method (1) and in 94% yield by the Perrier method (3). By the latter method 2-bromothiophene yielded 2-acetyl-5-bromothiophene in 77% conversion and quantitative yield.

Chlorination of 2-acetylthiophene gave 2-(chloroacetyl)thiophene in 41% conversion and 77% yield. Under the same conditions 2-acetyl-5-chlorothiophene gave 5-chloro-2-(chloroacetyl)thiophene in 62% yield. The compound also was prepared in 59% conversion and 73% yield from 2-chlorothiophene, chloroacetyl chloride, and aluminum chloride. 2-(Chloroacetyl)thiophene and 5-chloro-2-(chloroacetyl)thiophene reacted with potassium cyanide in aqueous ethanol to give the corresponding nitriles in 60% and 73% yields, respectively.

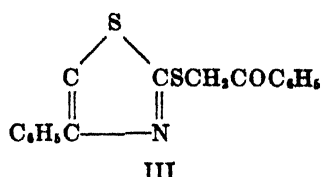
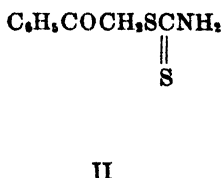
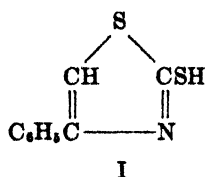
Treatment of 2-(chloroacetyl)thiophene with ammonium thiocyanate in ethanol gave 87% of 2-(thiocyanoacetyl)thiophene. Infra-red absorption spectra measurements on this compound showed bands at 6.14 microns and at 4.62 microns, which indicated the presence of a carbonyl and a thiocyano group, respectively. This compound liberated ammonia when boiled with aqueous sodium hydroxide and gave a negative chemical test for both the thiocyanate (9) and isothiocyanate (10) groups. It did not react with acetic anhydride or semicarbazide, but reacted slowly with 2,4-dinitrophenylhydrazine to give the corresponding 2,4-dinitrophenylhydrazone, which gave a positive test for the thiocyanate group.

Evidently under the influence of weak bases or heat the 2-(thiocyanoacetyl)thiophene cyclized to give 2-imino-5-(2'-thienyl)-1,3-oxathiole, so that, except in the case of the strongly acid 2,4-dinitrophenylhydrazine reagent, the chemical reactions observed were those of the oxathiole.



Under similar conditions thiocyanacetone gives 2-imino-5-methyl-1,3-oxathiole (11). 5-Chloro-2-(chloroacetyl)thiophene reacted with ammonium thiocyanate to give 90% of 5-chloro-2-(thiocyanoacetyl)thiophene. The structure of this last compound is formulated by analogy to 2-(thiocyanoacetyl)thiophene.

Before attempting the preparation of mercaptothienylthiazoles, the preparation of mercaptophenylthiazoles was examined. Miolati (12) condensed ω -bromoacetophenone with ammonium dithiocarbamate and obtained 2-mercapto-4-phenylthiazole (I). He found it desirable to treat his crude product with hydrogen chloride in boiling benzene to cyclize any S-phenacyldithiourethan (II). He also isolated a small amount of a by-product which he thought was phenacyldithiourethan. By operating at room temperature in ether solution Levi (13) prepared this dithiourethan and showed that on heating to 135° it lost water to give the mercaptothiazole. Ubaldini and Fiorenza (14) repeated Levi's work and obtained 70% of the phenacyldithiourethan and 30% of Miolati's by-product. When the reactants were allowed to stand for sixteen hours, 55% of the mercaptothiazole was obtained together with 45% of the by-product, which was shown to be phenacyl 4-phenyl-2-thiazolyl sulfide (III).



Mathes (15) reported a 95% yield of 2-mercapto-4-phenylthiazole by treating ω -chloroacetophenone with ammonium dithiocarbamate in aqueous solution.

We have found that by using ω -chloroacetophenone, which is less reactive than ω -bromoacetophenone, in any solvent such as ethanol, methanol, water, or ethylene glycol, in which ammonium dithiocarbamate is somewhat soluble, yields of 81–86% of 2-mercapto-4-phenylthiazole can be obtained. While our yields were somewhat lower than that obtained by Mathes (15), our crude product had an appreciably higher melting point. It was found desirable to boil the crude product with benzene to cyclize any phenacyldithiourethan. When this was not done, a small amount of its hydrolysis product, phenacyl mercaptan, appeared as a by-product. It probably was formed when the crude reaction product was treated with alkali to separate the mercaptan. With ω -bromoacetophenone more phenacyl 4-phenyl-2-thiazolyl sulfide was obtained than mercaptothiazole.

In ethanol solution 2-(chloroacetyl)thiophene reacted with ammonium dithiocarbamate to give 86% of 2-mercapto-4-(2'-thienyl)thiazole. Under the same conditions 5-chloro-2-(chloroacetyl)thiophene gave 91% of 4-(5'-chloro-2'-thienyl)-2-mercaptothiazole. With ether as the reaction medium, in which ammonium dithiocarbamate is insoluble, some of the corresponding sulfide was obtained in each case.

The authors are grateful to Mr. D. R. Beasecker and Mr. W. Noetling of this laboratory for the measurement and interpretation of the absorption spectra.

EXPERIMENTAL¹

2-Acetylthiophene was prepared by the method of Hartough and Kosak (1) in which thiophene and acetic anhydride were caused to react in the presence of a small amount of iodine. The yield was 86%, b.p. 89–91°/11 mm., (77–78°/4 mm.) (1), n_D^{25} 1.5644–1.5648 (n_D^{20} 1.5666) (1).

The semicarbazone was prepared by the method of Shriner and Fuson (16) in 93% yield. After one crystallization from 60% ethanol it melted at 188–189° (191–192°) (1).

2-Acetyl-5-chlorothiophene was prepared from 2-chlorothiophene, acetyl chloride, and aluminum chloride by a method previously described for 2-acetylthiophene (3). The yield of 2-acetyl-5-chlorothiophene was 94%, b.p. 117–118°/17 mm. A sample was crystallized twice from ethanol, m.p. 47° (52°) (17).

By the method of Hartough and Kosak (1) using equimolar quantities of 2-chlorothiophene and acetic anhydride in the presence of iodine, 2-acetyl-5-chlorothiophene was obtained in 71% conversion and 84% yield, b.p. 120–123°/21 mm.

2-Acetyl-5-bromothiophene, b.p. 103°/4 mm., was prepared from acetyl chloride and 2-bromothiophene in 77% conversion and quantitative yield. The procedure was identical to that employed for the preparation of 2-acetyl-5-chlorothiophene. An analytical sample of the product, crystallized from benzene-hexane, melted at 94–95° (94°) (17).

2-(Chloroacetyl)thiophene. In a 500-cc., three-necked flask equipped with a reflux condenser, stirrer, thermometer, and gas inlet tube was placed 378 g. of 2-acetylthiophene. Chlorine was introduced while the liquid was illuminated with a 100-watt incandescent lamp. After an induction period of fifteen minutes, during which time chlorine was absorbed and the temperature rose from 20° to 65°, the evolution of hydrogen chloride commenced. The introduction of chlorine was continued at a reaction temperature of 65–75° for eighty-five minutes when a weight gain of 63 g. was observed. The reaction mixture was distilled to give 406.3 g., b.p. 101–146°/19 mm. and 21.1 g. of residue. Fractionation of the distillate gave 177.1 g. (47% recovery) of 2-acetylthiophene, b.p. 73–81°/5 mm., n_D^{25} 1.5644; 21.6 g. of intermediate, b.p. 81–111°/5 mm., n_D^{25} 1.5744; 196.9 g. (41% conversion, 77% yield) of 2-(chloroacetyl)thiophene, b.p. 111–113°/5 mm.; and 6.5 g. of residue. The product solidified in the receiver. In another experiment a small sample, dried between sheets of filter paper, melted at 47–48° (48°) (18).

5-Chloro-2-(chloroacetyl)thiophene was prepared by a method previously described for 2-acetylthiophene (3) using aluminum chloride, chloroacetyl chloride, and 2-chlorothiophene in carbon tetrachloride at 12–25°. The conversion was 59% and the yield 73%, b.p. 94–98°/1 mm., m.p. 79–81°. After recrystallization from hexane the melting point was 80–81°.

5-Chloro-2-(chloroacetyl)thiophene also was prepared by chlorinating 104.2 g. of 2-acetyl-5-chlorothiophene in 150 cc. of boiling carbon tetrachloride. A weight gain of 20 g. was observed in fifty minutes' time. A stream of dry air was then blown through the hot solution for fifteen minutes. Upon cooling, there was obtained 71.2 g. of 5-chloro-2-(chloroacetyl)thiophene, m.p. 72–77°. When the filtrate was concentrated to one-half its original volume, an additional 7.1 g. was obtained, m.p. 78–79°, total yield 62%. A sample of the first crop was twice crystallized from benzene-hexane, m.p. 80–81°.

Anal. Calc'd for $C_6H_4Cl_2OS$: Cl, 36.4. Found: Cl, 36.6.

2-Thenoylacetonitrile. To a cold solution of 13.0 g. of potassium cyanide in 40 cc. of water was added with shaking a solution of 16.1 g. of 2-(chloroacetyl)thiophene in 50 cc. of ethanol. The ketone immediately precipitated. The mixture was allowed to stand for

¹ All melting points are corrected. The carbon-hydrogen and nitrogen analyses are micro combustions conducted by the Oakwold Laboratories, Alexandria, Virginia. Some of the sulfur determinations are by Oakwold; the remainder and the chlorine determinations are by P. J. Adams, Miss Margaret Magin and Miss Mary Neal of the Monsanto Chemical Company, Dayton 7, Ohio.

one hour with occasional shaking, during which time the maximum temperature was 33°. Water was then added to incipient turbidity followed by a few drops of 10% sodium hydroxide. After the mixture was twice extracted with small portions of benzene, Norit was added and the solution was filtered. The filtrate was cooled in ice and carefully acidified with cold 3 *N* hydrochloric acid. The precipitated 2-thenoylacetoneitrile was washed with cold water and dried in a vacuum desiccator over phosphorus pentoxide. It weighed 9.0 g. (60% yield), m.p. 120–128°. An analytical sample, after several crystallizations from ethanol melted at 136–137° (137°) (19).

Anal. Calc'd for C_7H_5NOS : N, 9.27. Found: N, 9.18.

2-Thenoylacetoneitrile dissolved in hot 25% sodium hydroxide with the liberation of ammonia. It gave a positive test with 2,4-dinitrophenylhydrazine reagent, but gave no semicarbazone when boiled for fifteen minutes with semicarbazide in 70% ethanol and did not react with malononitrile in the presence of piperidine.

5-Chloro-2-thenoylacetoneitrile. To a solution of 4.9 g. of potassium cyanide in 30 cc. of water, cooled by an ice-bath, there was added a solution of 7.0 g. of 5-chloro-2-(chloroacetyl)thiophene in 75 cc. of ethanol. The resulting suspension was removed from the ice-bath and shaken. The temperature was kept below 30° by occasional cooling. After thirty minutes, when solution was complete, the flask was placed in the refrigerator overnight. The mixture was diluted with 45 cc. of water to incipient turbidity, treated with a few drops of 10% sodium hydroxide and extracted three times with small portions of benzene. The aqueous solution was treated with Norit in the cold, filtered, and acidified with 3 *N* hydrochloric acid. The light brown crystals which precipitated were washed with cold water, and dried *in vacuo* over potassium hydroxide. This crude product weighed 4.9 g. (73% yield), m.p. 108–114°. After four recrystallizations from ethanol, in two of which the solution was treated with Norit, an analytical sample, comprising white crystals, melted at 120°.

Anal. Calc'd for C_7H_4ClNOS : Cl, 19.1. Found: Cl, 18.9.

2-(Thiocyanoacetyl)thiophene. A mixture of 32.1 g. of 2-(chloroacetyl)thiophene and 19.0 g. of ammonium thiocyanate in 300 cc. of absolute ethanol was placed in a 500-cc., three-necked flask equipped with a stirrer, thermometer, and condenser. After it had been stirred for one hour at room temperature, the mixture was heated gradually to the boiling point over a forty-five minute period. It was filtered hot and the precipitate was washed with a little hot ethanol. Upon cooling, the combined filtrate and washings deposited yellow-tan crystals of 2-(thiocyanoacetyl)thiophene. This precipitate was separated and dried, 29.5 g., m.p. 88–89°. The filtrate was evaporated nearly to dryness, cooled, and diluted with water. The gummy yellow precipitate thus obtained was recrystallized from ethanol to give an additional 2.4 g. (total yield 87%), m.p. 87–88°. An analytical sample from another preparation was crystallized three times from ethanol, m.p. 90–91° (88°) (20).

Anal. Calc'd for $C_7H_5NOS_2$: N, 7.65. Found: N, 7.92.

When boiled with 10% aqueous sodium hydroxide, 2-(thiocyanoacetyl)thiophene evolved a gas which turned moist litmus blue. The compound gave a negative test for both the thiocyanate (9) and isothiocyanate (10) groups. After standing for one-half hour with 2,4-dinitrophenylhydrazine reagent, a precipitate appeared. This was washed with ethanol, and dried. This compound gave a positive test for the thiocyanate group. An analytical sample was crystallized from a mixture of ethanol and ethyl acetate, m.p. 160–161°.

Anal. Calc'd for $C_{11}H_9N_3O_4S_2$: N, 19.3. Found: N, 19.9.

2-(Thiocyanoacetyl)thiophene was recovered unchanged when boiled for five minutes with acetic anhydride and when treated with semicarbazide in aqueous ethanol (16).

5-Chloro-2-(thiocyanoacetyl)thiophene. A mixture of 29.3 g. of 5-chloro-2-(chloroacetyl)thiophene and 15.2 g. of ammonium thiocyanate in 250 cc. of absolute ethanol was heated to 80° over a twenty-minute period and stirred at that temperature for an additional ten minutes. The precipitated ammonium chloride was washed twice with hot ethanol.

After the combined filtrate and washings were cooled, the white crystals were washed with water, and dried to give 22.3 g., m.p. 97–98°. Chilling of the combined filtrate and washings produced a second crop of 7.1 g., m.p. 89–92°. The total yield was 90%. An analytical sample from the first crop was crystallized twice from ethanol, m.p. 99°.

Anal. Calc'd for $C_7H_4ClNOS_2$: S, 29.5; Cl, 16.3.

Found: S, 29.0; Cl, 16.0.

2-Mercapto-4-phenylthiazole. To a suspension of 16.5 g. of ammonium dithiocarbamate in 50 cc. of absolute ethanol was added with shaking and cooling a mixture of 15.5 g. of phenacyl chloride and 100 cc. of absolute ethanol. After the initial reaction had subsided, the flask was stoppered and allowed to stand at room temperature with occasional shaking for seven days. The slurry of crystals was cooled by means of an ice-bath, diluted with 200 cc. of water and filtered. The precipitate was washed with water and dried. It was then heated under reflux with 150 cc. of benzene while the evolved water was collected in a Dean and Stark trap. The residue, obtained by evaporating the benzene, was treated with 150 cc. of 5% sodium hydroxide and filtered. The filtrate was cooled in an ice-bath and acidified with dilute hydrochloric acid. The resulting white precipitate was washed with water, and dried to give 16.5 g. (86%) of 2-mercapto-4-phenylthiazole, m.p. 167–169°. An analytical sample was crystallized from aqueous ethanol, m.p. 173–174° (170°) (13).

Anal. Calc'd for $C_8H_7NS_2$: S, 33.2; N, 7.25.

Found: S, 33.4; N, 7.45.

Yields of 81–83% of 2-mercapto-4-phenylthiazole were obtained when the reaction was conducted in water, methanol or ethylene glycol.

Phenacyl mercaptan. In a reaction similar to the above conducted in aqueous solution and in a reaction between phenacyl bromide and ammonium dithiocarbamate in ethanol, a small amount of yellow oil appeared when the alkaline solution of the mercaptothiazole was acidified. In both of these experiments the boiling with benzene was omitted. This oil was separated from the filtrate and the two samples were combined and distilled to give 3.5 g. of phenacyl mercaptan, b.p. 141–144°/14 mm. (116–122°/4 mm.), (21) n_D^{20} 1.5930.

The phenylhydrazone, prepared by the method of Shriner and Fuson (22), was crystallized three times from ethanol, m.p. 91–92° (90–91°) (21).

Phenacyl 4-phenyl-2-thiazolyl sulfide. A reaction similar to that described for the preparation of 2-mercapto-4-phenylthiazole was conducted with 16.5 g. of ammonium dithiocarbamate and 19.9 g. of phenacyl bromide in 200 cc. of water. The method for the isolation of the product was the same. The alkaline slurry, obtained by treating the product with 150 cc. of 5% sodium hydroxide, was filtered and the precipitate was washed with water. Acidification of the cooled, combined filtrate and washings with dilute hydrochloric acid precipitated crude 2-mercapto-4-phenylthiazole, which was washed with water, and dried, 3.3 g. (17% yield), m.p. 150–168°.

The residue from the filtration of the alkaline slurry was dried to give 11.8 g. (76% yield) of phenacyl 4-phenyl-2-thiazolyl sulfide, m.p. 111–116°. An analytical sample melted at 121° (115–117°) (14), after two recrystallizations from ethanol.

Anal. Calc'd for $C_{17}H_{13}NOS_2$: C, 65.6; H, 4.21; N, 4.50; S, 20.6.

Found: C, 65.4; H, 4.46; N, 5.01; S, 22.2.

When ethanol was substituted for water as the solvent for the initial condensation, the yields of 2-mercapto-4-phenylthiazole and phenacyl 4-phenyl-2-thiazolyl sulfide were 39% and 60%, respectively.

2-Mercapto-4-(2'-thienyl)thiazole. To a suspension of 16.5 g. of ammonium dithiocarbamate in 50 cc. of absolute ethanol was added with shaking a partial solution of 16.1 g. of 2-(chloroacetyl)thiophene in 100 cc. of absolute ethanol. The mixture warmed immediately and became yellow. It was cooled in an ice-bath for fifteen minutes until the reaction had subsided, and then was allowed to stand at room temperature with occasional shaking for four days. The slurry of yellow crystals was diluted with 200 cc. of water and cooled by an ice-bath. The solid was washed with water and treated with 125 cc. of cold 5% aqueous sodium hydroxide. Nearly all the solid dissolved. The mixture was filtered and the

filtrate was cooled and carefully acidified with dilute hydrochloric acid. The crude 2-mercapto-4-(2'-thienyl)thiazole was washed with water, and dried. It weighed 17.2 g. (86% yield), m.p. 173-176°. An analytical sample was crystallized from benzene and ethanol, m.p. 177°.

Anal. Calc'd for $C_7H_4NS_2$: N, 7.03; S, 48.3.

Found: N, 7.22; S, 48.4.

2'-Thenoylmethyl 4-(2''-thienyl)-2-thiazolyl sulfide. The reaction between 120.3 g. of 2-(chloroacetyl)thiophene and 82.5 g. of ammonium dithiocarbamate in 600 cc. of anhydrous ether was allowed to proceed for fifteen days at room temperature after the initial cooling. The solid was filtered and divided by treatment with 5% aqueous sodium hydroxide into 74.1 g. of alkali-soluble 2-mercapto-4-(2'-thienyl)thiazole, m.p. 176-177°, and 8.0 g. of alkali-insoluble 2'-thenoylmethyl 4-(2''-thienyl)-2-thiazolyl sulfide, m.p. 86-88°. After two crystallizations from ethanol, the first after treatment of the solution with Norit, an analytical sample of the latter compound melted at 89-90°.

Anal. Calc'd for $C_{11}H_9NOS_2$: N, 4.33; S, 39.7.

Found: N, 4.58; S, 39.7.

The ethereal filtrate was worked up similarly to obtain 4.8 g. of 2-mercapto-4-(2'-thienyl)thiazole, m.p. 164-168° after two crystallizations from aqueous ethanol (total yield 53%) and 4.2 g. of 2'-thenoylmethyl 4-(2''-thienyl)-2-thiazolyl sulfide, m.p. 88-89° after three crystallizations from ethanol (total yield 10%).

4-(5'-Chloro-2'-thienyl)-2-mercaptothiazole. To a suspension of 16.5 g. of ammonium dithiocarbamate in 50 cc. of absolute ethanol was added a mixture of 19.5 g. of 5-chloro-2-(chloroacetyl)thiophene and 100 cc. of absolute ethanol. The mixture was cooled by an ice-bath for a few minutes until the initial reaction had subsided, and then allowed to stand at room temperature with occasional shaking for seven days. The orange suspension of crystals was diluted with an equal volume of water and cooled by an ice-bath. The precipitate was washed thoroughly with water. Treatment with 175 cc. of 10% potassium hydroxide dissolved most of this solid. The alkaline mixture was filtered and the filtrate was cooled and carefully acidified with dilute hydrochloric acid. The precipitated 4-(5'-chloro-2'-thienyl)-2-mercaptothiazole was washed with water, and dried *in vacuo* over calcium chloride to give 20.7 g. (91% yield), m.p. 201°. An analytical sample was crystallized twice from ethanol, m.p. 205°.

Anal. Calc'd for $C_7H_4ClNS_2$: S, 41.2; Cl, 15.2.

Found: S, 41.4; Cl, 15.1.

5'-Chloro-2'-thenoylmethyl 4-(5''-chloro-2''-thienyl)-2-thiazolyl sulfide. The reaction between 39.0 g. of 5-chloro-2-(chloroacetyl)thiophene and 33.0 g. of ammonium dithiocarbamate was allowed to proceed for four days at room temperature in 250 cc. of ether. Part of the 4-(5'-chloro-2'-thienyl)-2-mercaptothiazole was separated from the crude reaction product by treatment with 5% sodium hydroxide. The remainder of the separation was effected with hot benzene and hot ethanol. The mercaptan was fairly soluble in the ethanol and insoluble in the benzene, whereas the sulfide showed the opposite solubility. By these means there was isolated 16.3 g. (35% yield) of crude 4-(5'-chloro-2'-thienyl)-2-mercaptothiazole and 8.3 g. (21% yield) of 5'-chloro-2'-thenoylmethyl 4-(5''-chloro-2''-thienyl)-2-thiazolyl sulfide. An analytical sample of the latter compound was crystallized several times from benzene, m.p. 133-134°.

Anal. Calc'd for $C_{13}H_7Cl_2OS_2$: S, 32.7; Cl, 18.1.

Found: S, 32.7; Cl, 17.6.

SUMMARY

The preparations of 2-(chloroacetyl)thiophene and of 5-chloro-2-(chloroacetyl)thiophene, have been described and their reactions with potassium cyanide, ammonium thiocyanate and ammonium dithiocarbamate have been

examined. In connection with the ammonium dithiocarbamate reactions, the corresponding phenacyl chloride chemistry also was reexamined.

DAYTON 7, OHIO.

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2-VINYLTHIOPHENES

WILLIAM S. EMERSON AND TRACY M. PATRICK, JR.

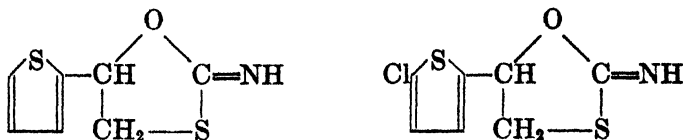
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The preparation of 2-vinylthiophene (1) by the reduction of 2-acetothienone and then the dehydration of the resulting carbinol has been examined in detail (2, 3). The highest yield obtained was 54% based on thiophene (2). More recent methods involve the low-temperature condensation of vinyl chloride with 2-thienylmagnesium bromide in the presence of cobaltous chloride to give a 29% yield of 2-vinylthiophene (4) and the dehydration of 2-(2-thienyl)ethanol (from thienylsodium and ethylene oxide) by means of molten potassium hydroxide to give a 38% yield based on 2-chlorothiophene (5). We have studied an alternate route, namely chloroethylation of thiophene with paraldehyde and hydrogen chloride, followed by dehydrochlorination with pyridine. By a careful control of conditions, 2-vinylthiophene has been obtained in 44% conversion and 50% yield. In this same way 5-chloro-2-vinylthiophene has been prepared in 24% conversion and 47% yield and 5-bromo-2-vinylthiophene in 20% conversion and 44% yield from the corresponding halogenated thiophenes.

When an attempt was made to pyrolyze 2-(α -chloroethyl)thiophene over calcium sulfate in order to obtain 2-vinylthiophene, the pyrolysis tube plugged almost immediately. Treatment with alcoholic sodium hydroxide gave mostly 2-(α -ethoxyethyl)thiophene and a little α -(2-thienyl)ethyl ether.

Dibromides have been prepared from all three vinylthiophenes, although that from 2-vinylthiophene decomposed and turned purple on standing in air. While 2-vinylthiophene has been titrated by the Kaufmann method (1), the isolation and properties of the resulting dithiocyanate have not been reported. We have prepared and characterized dithiocyanates from all three vinylthiophenes by treating 2-vinylthiophene and 5-chloro-2-vinylthiophene with thiocyanogen in anhydrous benzene and by treating 5-bromo-2-vinylthiophene with thiocyanogen in glacial acetic acid. When the acetic acid method was applied to the first two compounds mentioned, products were obtained whose empirical formulas corresponded to hypothiocyanous acid addition products of the vinylthiophenes. That from 5-chloro-2-vinylthiophene was examined in detail. It gave negative tests for both the thiocyanate and isothiocyanate groups and evolved ammonia when heated with 25% aqueous sodium hydroxide. After the last test no sulfide ion was found in the solution and acidification and boiling of another hydrolyzed sample caused carbon dioxide to be evolved. Infra-red absorption spectra showed no band at 4.62 microns, which wave length is characteristic for the thiocyno group. A strong band at 6.04 microns can be identified as either a C=N or NH₂ band. A band at 9.14 microns has two possibilities, C—N—C or C—O—

C. By analogy with the behavior of thiocyanacetone (6) these compounds are probably iminoxathiolanes:



Since these products were obtained either by hydrolysis of the corresponding dithiocyanates or by the addition of hypothiocyanoous acid to the vinyl compounds, the oxygen is probably attached to the α -carbon atom. This configuration is favored by the known reactivity of groups in the α -position to thiophene and benzene and by analogy to the mode of addition of hypohalous acids to styrene.

In the preparation of 5-chloro-2-vinylthiophene dithiocyanate a compound believed to be 5-chloro-2-(α -isothiocyano- β -thiocyanoethyl)thiophene also was isolated. It gave a positive test for both the thiocyanate and isothiocyanate groups and the same analysis as the dithiocyanate. Since thenyl thiocyanate readily rearranges to the isothiocyanate (7), it probably is the α -thiocyano group which has rearranged in this case.

5-Chloro-2-vinylthiophene did not add di-*p*-tolyl disulfide in the presence of iodine in anhydrous ether according to the procedure of Holmberg (8). Treatment of 2-vinylthiophene with calcium hypochlorite and carbon dioxide (9) with the object of obtaining the chlorohydrin gave a compound whose analysis and complete inertness to hydrolytic agents suggest it to be β ,5-dichloro-2-vinylthiophene. The compound was unsaturated and oxidation with neutral potassium permanganate gave 5-chloro-2-thiophenecarboxylic acid. 5-Chloro-2-vinylthiophene chlorohydrin probably was an intermediate, since in one preparation water was given off during the first part of the distillation. Ring chlorination of thiophene with hypochlorous acid has been observed previously (10).

The authors are grateful to Mr. D. R. Beasecker and Mr. W. Noetling of this laboratory for the absorption spectra measurements and their interpretation.

EXPERIMENTAL

2-Vinylthiophene. In a 1-liter, three-necked flask were placed 336 g. of thiophene, 176 g. of paraldehyde, and 300 cc. of concentrated hydrochloric acid. While this mixture was stirred and maintained at 10–13° by an ice-salt bath, hydrogen chloride was bubbled in over a thirty-five minute period, at the end of which the solution was saturated. The contents of the flask were poured on ice, the layers were separated, and the organic portion was washed three times with 200-cc. portions of ice-water. This layer was then added with cooling to 316 g. of pyridine containing 2.0 g. of α -nitroso- β -naphthol. After the mixture had stood for one and one-half hours, it was distilled and three fractions were collected at successively lower pressures, the last two over α -nitroso- β -naphthol: I to 70°/175 mm., II to 82°/100 mm., and III to 125°/50 mm. These distillates were combined and poured onto a mixture of ice and 400 cc. of concentrated hydrochloric acid. The layers were separated and the organic portion was washed with very dilute hydrochloric acid and then with very dilute ammonia. After drying over Drierite, the product was filtered and fractionated to give 45.6 g. (13.5% recovery) of thiophene, b.p. 36–47°/150 mm., n_D^{20} 1.5266; 11.8 g. of inter-

mediate, b.p. 47°/150 mm. to 81°/100 mm., n_D^{20} 1.5400; and 191.3 g. (44% conversion, 50% yield) of 2-vinylthiophene, b.p. 65–67°/50 mm. (62–63°/50 mm.) (1, 2), n_D^{20} 1.5710 (n_D^{20} 1.5698) (2). There was a residue of 22.9 g.

In a similar run starting with 84 g. of thiophene, the crude 2-(α -chloroethyl)thiophene was dropped into a tube containing calcium sulfate held at 400–425°. The tube plugged almost immediately. The remainder of the crude 2-(α -chloroethyl)thiophene was added over a one-half-hour period to a solution of 60 g. of sodium hydroxide in 276 cc. of ethanol and 74 cc. of water. After an additional one-half hour at 50–60°, the mixture was poured into 1 liter of water and then extracted three times with benzene. The combined extracts were filtered and distilled to give 61 g. (39%) of 2-(α -ethoxyethyl)thiophene, b.p. 130–150°/170 mm., n_D^{20} 1.5020; 9 g. (7%) of what may be 2-(α -hydroxyethyl)thiophene, b.p. 108–135°/21 mm. (90–103°/14 mm.) (1), n_D^{20} 1.5284 (n_D^{20} 1.5399) (1); and 24 g. (20%) of α -(2-thienyl)ethyl ether, b.p. 135–192°/21 mm., n_D^{20} 1.5505.

An analytical sample of 2-(α -ethoxyethyl)thiophene boiled at 78–79°/16 mm., n_D^{20} 1.4963, d_4^{20} 1.021.

*Anal.*¹ Calc'd for $C_8H_{12}OS$: C, 61.5; H, 7.69.

Found: C, 62.1; H, 7.99.

An analytical sample of α -(2-thienyl)ethyl ether boiled at 150–160°/16 mm. (121–122°/3 mm.) (1), n_D^{20} 1.5754 (n_D^{20} 1.5580) (1), d_4^{20} 1.151.

*Anal.*¹ Calc'd for $C_{12}H_{14}OS_2$: C, 60.5; H, 5.88.

Found: C, 62.0; H, 5.75.

2-Vinylthiophene dibromide was prepared by treating 11 g. of 2-vinylthiophene in 100 cc. of carbon tetrachloride with 5 cc. of bromine in 50 cc. of carbon tetrachloride. The solutions were mixed at ice-bath temperature. Evaporation of the carbon tetrachloride left 21 g. (78%) of 2-vinylthiophene dibromide, a white solid which turned purple on standing in air. An analytical sample was crystallized twice from hexane, m.p. 47–50°. This melting point and all others are corrected.

*Anal.*² Calc'd for $C_6H_6Br_2S$: Br, 59.3. Found: Br, 59.6.

2-Vinylthiophene dithiocyanate. A solution of thiocyanogen in dry benzene was prepared by treating an ice-cold suspension of 194 g. of lead thiocyanate in 300 cc. of benzene with a cold solution of 80 g. of bromine in 300 cc. of benzene. The solid was separated and washed with 150 cc. of benzene. Fifty-five grams of 2-vinylthiophene was added to the filtrate and the solution was allowed to stand all day in the bright sunlight. It was then seeded and placed in an ice-box overnight. The first crop of crystals was separated, and the filtrate was evaporated under reduced pressure at room temperature to a thick syrup. Additional product was filtered from this syrup. The total yield of crude 2-vinylthiophene dithiocyanate was 64 g. (57%). An analytical sample was crystallized four times by dissolving in benzene and precipitating with hexane, m.p. 87°.

*Anal.*¹ Calc'd for $C_6H_6N_2S_2$: N, 12.4. Found: N, 12.3.

This compound and a number of those following were tested for the presence of the thiocyanate (11) group by boiling a small amount of the solid for three to five minutes with 10% aqueous sodium hydroxide. After cooling, the mixture was acidified with dilute sulfuric acid and a small amount of 1% ferric chloride was added. The appearance of a blood red color constituted a positive test, which was given by vinylthiophene dithiocyanate.

These compounds also were tested for the presence of the isothiocyanate (12) group by shaking a small amount of the solid with aqueous ammoniacal silver nitrate. If necessary the mixture was heated. A black precipitate, which was not obtained with vinylthiophene dithiocyanate, constituted a positive test.

Treatment of 2-vinylthiophene with bromine and potassium thiocyanate in glacial acetic acid, followed by dilution with water, gave an orange solid. Digestion of this material with boiling ethanol extracted a solid, m.p. 140–141° after three crystallizations from ethanol. It is believed to be 5-(2'-thienyl)-2-imino-1,3-oxathiolane.

¹ Microanalyses performed by the Oakwold Laboratories, Alexandria, Virginia.

² Analysis by Mr. Donald Stoltz, Monsanto Chemical Co., Dayton, Ohio.

*Anal.*¹ Calc'd for $C_7H_7NOS_2$: C, 45.4; H, 3.78; N, 7.57.

Found: C, 45.5; H, 4.02; N, 7.85.

β ,5-Dichloro-2-vinylthiophene. In a 2-l., three-necked flask, equipped with a stirrer, thermometer, reflux condenser, dropping-funnel, and gas inlet tube, were placed 55 g. of 2-vinylthiophene, 750 cc. of water, and a trace of Sterox (Monsanto non-ionic synthetic detergent). While this stirred mixture was held at 18–20° by running water, a solution of 82 g. of H.T.H. (a commercial product containing about 70% calcium hypochlorite) in 750 cc. of water was added over a ten-hour period. Carbon dioxide was introduced during the addition. After a twelve-hour period of additional stirring, sodium bisulfite was added, and the mixture was filtered to remove calcium carbonate. A brown oil was separated from the filtrate. The precipitate was washed four times with benzene and each wash was used to extract the filtrate. The combined oil and washings were dried over anhydrous sodium sulfate. Distillation yielded 45 g. (50% based on thiophene or 64% based on H.T.H.) of β ,5-dichloro-2-vinylthiophene, b.p. 80°/4–2 mm., n_D^{25} 1.6150. An analytical sample boiled at 116–118°/18 mm., n_D^{25} 1.6169, d_4^{25} 1.3885, m.p. 16–18°.

Anal. Calc'd for $C_6H_4Cl_2S$: C, 40.2; H, 2.25; Cl, 39.6.

Found: C, 40.7; H, 2.55; Cl, 39.6.

When 27.3 g. of β ,5-dichloro-2-vinylthiophene was boiled for six hours with 18.9 g. of sodium acetate in 75 cc. of water, 24.5 g. (90%) was recovered unchanged, b.p. 64–66°/1.5 mm., n_D^{25} 1.6168. Treatment of 54.6 g. with 15 g. of calcium carbonate suspended in 150 cc. of water for six hours at 120° in an autoclave yielded a 40.5-g. (74%) recovery, b.p. 76–81°/3 mm., n_D^{25} 1.6163–1.6171. Similarly when 40.0 g. was boiled for thirteen hours with 20.5 g. of sodium acetate in 50 cc. of water and 250 cc. of acetone, the recovery was 31.1 g. (77%), b.p. 76–78°/3 mm., n_D^{25} 1.6171–1.6178.

β ,5-Dichloro-2-vinylthiophene decolorized a solution of bromine in carbon tetrachloride and the vapors did not fume in moist air. Oxidation with neutral potassium permanganate gave 5-chloro-2-thiophenecarboxylic acid, m.p. 151–152° (146–147°) (13).

*5-Chloro-2-vinylthiophene*⁴ was prepared in the same way as 2-vinylthiophene, starting with 355.5 g. of 2-chlorothiophene, 132 g. of paraldehyde and 225 cc. of concentrated hydrochloric acid. Thirty minutes was required for the saturation with hydrogen chloride and the gas was introduced for another twenty minutes at a maximum temperature of 9°. The distillation from 237 g. of pyridine was conducted to 130°/25 mm. The final distillation yielded 176 g. (50%) of recovered 2-chlorothiophene, b.p. 49–52°/50 mm., n_D^{25} 1.5438; 11.5 g. of intermediate, b.p. 35–73°/20 mm., n_D^{25} 1.5502; and 103.5 g. (24% conversion, 47% yield) of 5-chloro-2-vinylthiophene, b.p. 73–78°/20 mm., n_D^{25} 1.5814. The residual clear, amber resin weighed 55 g. An analytical sample of 5-chloro-2-vinylthiophene boiled at 83.9–84.0°/30 mm., n_D^{25} 1.5820, d_4^{25} 1.206.

*Anal.*¹ Calc'd for C_6H_5ClS : S, 22.2; Cl, 24.5.

Found: S, 22.4; Cl, 24.7.

5-Chloro-2-vinylthiophene dibromide was prepared by adding over a one and one-half-hour period a solution of 48 g. of bromine in 50 cc. of carbon tetrachloride to a solution of 40 g. of 5-chloro-2-vinylthiophene in 300 cc. of carbon tetrachloride held at –5° to –1°. Evaporation of the carbon tetrachloride left 82.7 g. (88%) of 5-chloro-2-vinylthiophene dibromide, m.p. 76°. An analytical sample, after two crystallizations from hexane, showed the same melting point.

*Anal.*¹ Calc'd for $C_6H_5Br_2S$: C, 23.7; H, 1.66.

Found: C, 23.8; H, 1.92.

5-Chloro-2-vinylthiophene dithiocyanate was prepared in the same way as 2-vinylthiophene dithiocyanate starting with 50.6 g. of 5-chloro-2-vinylthiophene and using a thiocyanogen

³ Analysis by Miss Mary Neal, Monsanto Chemical Co., Dayton, Ohio.

⁴ Since the acceptance of this manuscript an article has appeared by Bachman and Heisey, *J. Am. Chem. Soc.*, **70**, 2378 (1948) describing the properties of these compounds and their preparation by alternative routes.

solution made from 125 g. of lead thiocyanate in 250 cc. of anhydrous benzene and 56 g. of bromine in 300 cc. of anhydrous benzene. The initial precipitate and that obtained by diluting the filtrate with hexane weighed 47.5 g., m.p. 97–98°, and constituted a 52% yield of 5-chloro-2-vinylthiophene dithiocyanate. An analytical sample melted at 99° after two crystallizations from benzene-hexane.

*Anal.*¹ Calc'd for $C_6H_5ClN_2S_2$: C, 36.9; H, 1.93.

Found: C, 36.8; H, 1.89.

5-Chloro-2-vinylthiophene dithiocyanate gave a positive test for thiocyanate and a negative test for isothiocyanate.

When the original benzene-hexane solution was evaporated to dryness, there remained a crystalline solid which weighed 35.8 g. after washing with ethanol and drying. It was recrystallized from benzene-hexane and then from hexane, m.p. 65°. This compound gave a positive test for both thiocyanate and isothiocyanate and represented a 39% yield of 5-chloro-2-(α -isothiocyano- β -thiocyanoethyl)thiophene.

*Anal.*¹ Calc'd for $C_8H_5ClN_2S_4$: C, 36.9; H, 1.93; N, 10.74.

Found: C, 37.3; H, 2.10; N, 10.69.

As with 2-vinylthiophene, treatment of 5-chloro-2-vinylthiophene with potassium thiocyanate and bromine in glacial acetic acid yielded 5-chloro-2-vinylthiophene dithiocyanate (18%) and a compound believed to be 5-[5'-chloro-2'-thienyl]-2-imino-1,3-oxathiolane (32%) which melted at 145° after two crystallizations from benzene.

*Anal.*¹ Calc'd for $C_7H_4ClNOS_2$: C, 38.3; H, 2.76; N, 6.38; S, 20.2.

Found: C, 38.2; H, 2.79; N, 6.80; S, 29.7.

5-[5'-Chloro-2'-thienyl]-2-imino-1,3-oxathiolane gave a negative test for both thiocyanate and isothiocyanate. On boiling with 25% aqueous sodium hydroxide, the compound dissolved, and the evolved vapors turned red litmus paper blue. Subsequent addition of lead acetate gave no black precipitate of lead sulfide. Acidification and boiling of another hydrolysis solution evolved a gas which gave a white precipitate with barium hydroxide.

*5-Bromo-2-vinylthiophene.*⁴ The chloroethylation was conducted in the same manner as for 2-vinylthiophene except that the 88 g. of paraldehyde was dropped over a forty-five-minute period into the mixture of 326 g. of 2-bromothiophene and 150 cc. of concentrated hydrochloric acid during the introduction of the hydrogen chloride. The dehydrochlorination was effected with 158 g. of pyridine and the mixture was distilled to 105°/25 mm. The residue was cooled and washed with water and the organic layer separated and distilled to 100°/15 mm. After the usual washing, fractionation of the combined distillates yielded 96.9 g. of 2-bromothiophene, b.p. 57–73°/30 mm., n_D^{20} 1.5753; 62.4 g. of intermediate, b.p. 73–90°/30 mm., n_D^{20} 1.5908; and 58 g. of 5-bromo-2-vinylthiophene, b.p. 90–103°/30 mm., n_D^{20} 1.6083. Assuming the refractive index of the intermediate to be proportional to the two components present, the intermediate contained 45.5 g. of 2-bromothiophene and 16.9 g. of 5-bromo-2-vinylthiophene. The recovery was, therefore, 142.4 g. (44%) and the conversion 74.9 g. (20%) with a 35% yield. Pure 5-bromo-2-vinylthiophene boiled at 85–87°/16 mm., n_D^{20} 1.6098, d_4^{20} 1.5259.

*Anal.*¹ Calc'd for C_6H_5BrS : C, 38.1; H, 2.67.

Found: C, 38.3; H, 2.99.

5-Bromo-2-vinylthiophene dibromide was prepared from 2.0 g. of 5-bromo-2-vinylthiophene by dissolving the compound in carbon tetrachloride and adding a slight excess of bromine in carbon tetrachloride. Evaporation of the solution left a quantitative yield of 5-bromo-2-vinylthiophene dibromide, m.p. 80–82°. An analytical sample melted at 83° after two crystallizations from hexane.

*Anal.*¹ Calc'd for $C_6H_3Br_2S$: C, 20.7; H, 1.44.

Found: C, 21.2; H, 2.05.

5-Bromo-2-vinylthiophene dithiocyanate was prepared by adding a solution of 1.9 g. of 5-bromo-2-vinylthiophene in 5 cc. of glacial acetic acid to a solution of 2.5 g. of potassium thiocyanate in 35 cc. of acetic acid. Then a solution of 1.6 g. of bromine in 10 cc. of acetic

acid was added slowly with shaking. After standing for a short time, the mixture was diluted with water, the precipitate separated, and then leached with hot ethanol. When this extract was chilled, 1.3 g. (43%) of 5-bromo-2-vinylthiophene dithiocyanate separated as yellow crystals, m.p. 94–95°. It was recrystallized twice from benzene-hexane, m.p. 96°.

*Anal.*¹ Calc'd for $C_6H_4BrN_2S_2$: C, 31.5; H, 1.65.

Found: C, 31.8; H, 1.94.

SUMMARY

Thiophene, 2-chlorothiophene, and 2-bromothiophene have been chloroethylated by treatment with paraldehyde and hydrogen chloride followed by dehydrochlorination with pyridine to give, respectively, 2-vinylthiophene, 5-chloro-2-vinylthiophene, and 5-bromo-2-vinylthiophene.

Dibromides and dithiocyanates have been prepared from each of these vinylthiophenes. In the preparation of dithiocyanates from 2-vinylthiophene and 5-chloro-2-vinylthiophene in glacial acetic acid as a solvent, some of the corresponding 5-thienyl (or chlorothienyl)-2-imino-1,3-oxathiolanes appeared as by-products.

Treatment of 2-vinylthiophene with hypochlorous acid gave β ,5-dichloro-2-vinylthiophene instead of the expected 2-vinylthiophene chlorohydrin.

DAYTON 7, OHIO.

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THE BENZOYLATION OF 2-AMINOPYRIDINE¹

ERNEST H. HUNTRESS AND HENRY C. WALTER²

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During studies (1) on the Beckmann rearrangement of the oximes of 2-benzoylpyridine, necessity arose for the characterization of 2-(benzoylamino)pyridine. Although this compound has been previously reported by five different laboratories, the record disclosed a distressing lack of accord.

2-(Benzoylamino)pyridine was first reported (2) from 2-aminopyridine by reaction with benzoyl chloride and aqueous alkali and next (3) by reaction with benzoic anhydride. The compound was claimed to melt at 165° (2, 3), to form a picrate salt, m.p. 146° (2) and both the supposed benzoyl derivative and its salt gave, respectively, appropriate analyses (2). Despite the concordance of these results both reports were completely erroneous.

Subsequent studies by Tschitschibabin and Bylinkin (4), completely confirmed by Wibaut and Dingemanse (5), utilized both methods but obtained 2-(benzoylamino)pyridine of m.p. 87° and 2-(dibenzoylamino)pyridine of m.p. 166–167°. The latter was readily hydrolyzed with dilute sodium carbonate to the former.

This apparent resolution of the earlier errors was soon complicated by a German patent (6) which claimed that 2-aminopyridine with benzoic anhydride gave 2-(dibenzoylamino)pyridine, m.p. 94–95°, and by a report (7) that carbodi-(2-pyridyl)imide with benzoic acid gave 2-(benzoylamino)pyridine, m.p. 80°. Still later 2-aminopyridinium benzoate was reported (8) as melting 145–146°.

By Schotten-Baumann benzylation of 2-aminopyridine we have obtained 2-(dibenzoylamino)pyridine, m.p. 167.5–169° uncor., confirming the Russian (4) and Dutch (5) reports. Hydrolysis with alcoholic sodium carbonate yielded 2-(benzoylamino)pyridine as earlier reported (4) but this product melted sharply at 82–83° uncor., and no higher value has ever been obtained for it in our work. This same 2-(benzoylamino)pyridine was also obtained (1) by Beckmann rearrangement of *syn*-phenyl 2-pyridyl ketoxime using thionyl chloride.

Contrary to the earlier reports (3, 4, 5), the reaction of 2-aminopyridine with benzoic anhydride gave in our hands 2-aminopyridinium benzoate, m.p. 145–146° uncor. [recorded (8) 145–146°], and the benzoate salt of 2-(benzoylamino)pyridine, m.p. 93.5–94.5° previously described (6) as 2-(dibenzoylamino)pyridine. Both these salts titrated sharply with alkali, giving appropriate neutralization equivalents, while the true 2-(dibenzoylamino)pyridine did not titrate with alkali at all. The identity of the 2-(benzoylamino)pyridinium benzoate, m.p. 93.5–94.5° was further confirmed by isolation of both components and by reprecipitation from them.

¹ This paper is constructed from part of a dissertation submitted by Henry C. Walter to the Faculty of the Massachusetts Institute of Technology in September, 1946, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

² du Pont Fellow: June–December, 1943; November, 1945–June, 1946. Present address: E. I. du Pont de Nemours, Jackson Laboratory.

The picrate salt of 2-(benzoylamino)pyridine was reported by the Russian (4) laboratory as melting at 193°, but by Zetsche (7) and Marckwald (2) at 146°. The picrate prepared from our 2-(benzoylamino)pyridine first melted 156–157° uncor., but after recrystallization changed to 196–198° uncor.

EXPERIMENTAL

2-(Dibenzoylamino)pyridine. 2-Aminopyridine (0.94 g. = 0.01 mole) was shaken at room temperature with benzoyl chloride (3.6 g. = 0.025 mole) and excess aqueous 10% sodium hydroxide solution. After disappearance of the odor of acyl halide the crude product amounted to 2.79 g. (92.5% yield). Several recrystallizations from ethanol yielded white needles, m.p. 167.5–169° uncor.

Anal. Calc'd for $C_{19}H_{14}N_2O_2$: N, 9.27. Found: N, 9.34, 9.38.

2-(Benzoylamino)pyridine. A sample of the above N,N-(dibenzoyl)-2-aminopyridine refluxed for thirty minutes with dilute ethanol containing a little sodium carbonate completely dissolved. On cooling, the solution deposited white needles (m.p. 81–83° uncor.) which on further recrystallization melted at 82–83° uncor.

Anal. Calc'd for $C_{13}H_{10}N_2O$: N, 14.14. Found: N, 14.1, 14.2.

The compound is appreciably soluble in aqueous alkali, from which it is precipitated by acetic acid. With ethanolic picric acid it yields a picrate salt, yellow needles from ethanol, m.p. 196–198° uncor.

2-(Benzoylamino)pyridinium chloride. A solution of 2-(benzoylamino)pyridine (1.5 g.) in dry ether (50 ml.) was treated with hydrogen chloride gas. The salt (1.61 g. = 91% yield) precipitated as fine white needles, m.p. 181–185° uncor. After several recrystallizations by precipitation from absolute ethanol by addition of dry ether, the salt melted 190.5–192.5° uncor. after sintering at 185–190°. The compound is readily soluble in water but insoluble in ether.

Anal. Calc'd for $C_{12}H_{11}ClN_2O$ (i.e., $C_{12}H_{10}N_2O \cdot HCl$): Cl, 15.14; Neut. Equiv., 234.5.

Found: Cl, 15.06, 15.15; Neut. Equiv., 234.3, 234.8

Reaction of 2-aminopyridine with benzoic anhydride. 2-Aminopyridine (2.82 g. = 0.03 mole) and benzoic anhydride (4.52 g. = 0.02 mole) dissolved in dry ether (50 ml.), on standing for 2 days at room temperature deposited hexagonal prisms melting at 145–148°. Evaporation of the ether gave a mixture of crystals and oil, the latter being readily dissolved by a little ether. The crystals of 2-aminopyridine benzoate (2.90 g. = 67% yield) after further purification melted 146–147° uncor.

Anal. Calc'd for $C_{12}H_{12}N_2O_2$ (i.e., $C_6H_6N_2 \cdot C_6H_5COOH$): Neut. Equiv., 216

Found: Neut. Equiv., 214.8, 215.9.

Evaporation of the ether solution left a colorless oil which soon solidified. After repeated recrystallization from dilute ethanol, long, thin, white flakes of 2-(benzoylamino)pyridinium benzoate, m.p. 93.5–94.5° uncor. were obtained.

Anal. Calc'd for $C_{19}H_{16}N_2O_3$ (i.e., $C_{12}H_{10}N_2O \cdot C_6H_5COOH$): N, 8.75; Neut. Equiv., 320.

Found: N, 8.81, 8.88; Neut. Equiv., 320, 321.

Upon shaking with dilute hydrochloric acid and ether, the salt gave 94% yield of benzoic acid. The aqueous layer eventually yielded 2-(benzoylamino)pyridine, m.p. 81–82°. These products failed to depress the melting points of authentic samples. Finally, a sample of the salt synthesized from 2-(benzoylamino)pyridine with benzoic acid, melted at 93–94° uncor. and did not depress the melting point of the material obtained from 2-aminopyridine and benzoic anhydride.

SUMMARY

1. Benzoylation of 2-aminopyridine by the Schotten-Baumann method gives in excellent yield 2-(dibenzoylamino)pyridine.

2. Reaction of 2-aminopyridine with benzoic anhydride in ether effects *mono*-benzoylation and both the 2-(benzoylamino)pyridine and the corresponding amount of 2-aminopyridine are obtained in the form of their benzoate salts.

3. Several anomalies in prior reports of 2-aminopyridine derivatives have been resolved.

CAMBRIDGE 39, MASS.

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CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. XXI. CHONDRILLASTEROL

WERNER BERGMANN AND FRANK H. McTIGUE¹

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Chondrilla nucula Schmidt is probably the most ubiquitous sponge of the shallow waters of the Bermuda Archipelago. Unlike most other common sponges it is very dense, and in shape, size, and color reminiscent of a chicken liver. The contents of fatty materials of this sponge are shown in Table I.

The crude sterol obtained from *Chondrilla* was dextrorotatory and gave a positive Tortelli-Jaffé (1) reaction. It was at once benzooylated, and the benzoates were subjected to a series of fractional recrystallizations. There were eventually obtained two fractions, of which the least soluble, m.p. 195°, represented the benzoate of a sterol different from all other sterols which have so far been described. Since the sterol was first isolated from *Chondrilla*, it is proposed to name it chondrillasterol. The properties of this sterol and of some of its derivatives are shown in Table II.

Titration with perbenzoic acid proved the sterol to be diunsaturated. Its strongly positive Tortelli-Jaffé reaction, its rotation and those of its derivatives (2) coupled with the fact that the melting point of the acetate is higher than that of the sterol (3) at once suggested the absence of a $\Delta^{5,6}$ and the presence of a $\Delta^{7,8}$ double bond. Since the data also indicated unsaturation in the sidechain, it was assumed that chondrillasterol possessed a structure analogous to that of α -spinasterol, stellasterol, and dihydroergosterol (2).

In accordance with these views, chondrillasteryl acetate readily took up one mole of hydrogen upon catalytic hydrogenation in an acidic medium to give the expected α -chondrillastenyl acetate (Table II). Rearrangement of the α -acetate by hydrogen chloride to the β -acetate and catalytic hydrogenation of the latter gave a stanyl acetate which was converted into the stanol. The properties of chondrillastanol (Table II) and its acetate were so similar to those of poriferastanol and its acetate (4) as to suggest the identity of the two stanols.

Further evidence indicating the relationship between chondrillasterol and poriferasterol was obtained from the results of the ozonolysis of chondrillasteryl acetate. It gave a volatile aldehyde which was isolated in the form of its 2,4-dinitrophenylhydrazone. This slightly dextrorotatory compound was identical with the corresponding derivative of the ethylisopropyl acetaldehyde which had previously been obtained by ozonolysis of poriferasteryl acetate (5).

The observations outlined above prove that the structural formula of chondrillasterol is that of $\Delta^7,8; 22,23$ poriferastadienol-3 (I). Since Fernholz (6) and

¹ The authors express their gratitude to the Emergency Science Research Fund of the Sheffield Scientific School, Yale University for a grant which has made possible the collection and extraction of sponge material at the Bermuda Biological Station during the summer of 1947.

TABLE I
COMPOSITION OF DRIED *Chondrilla nucula**

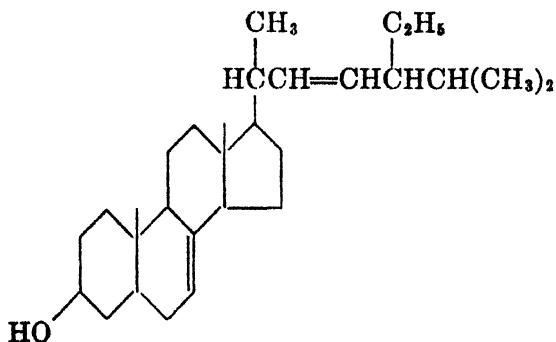
FRACTION	TOTAL SPONGE	ORGANIC MATTER, %	FAT	UNSATON. MATTER
Spicules.....	0.5			
Organic.....	99.5	100		
Fat.....	3.5	3.5	100	
Unsat. Matter.....	1.45	1.45	40.5	100
Sterol.....	1.25	1.25	35.5	86

* See explanation in experimental section.

TABLE II

DERIVATIVE	M.P. °C	$[\alpha]_D^{25}$	$[M]_D^{25}$
Sterol.....	168-169	-1.1	-4
Acetate.....	175-176	-1	-5
Benzoate.....	194-195	+4	+21
α -Stenyl acetate.....	111-112	+8.9	+41
Stanol (Poriferastanol).....	142-143	+22.5	+93
Stanyl acetate.....	139-140	+15	+69

Barton (2) have shown that α -spinasterol possesses a similar structure, and since it has been demonstrated in a previous study that stigmasterol and poriferasterol are C_{24} -epimers, it follows that chondrillasterol is the C_{24} -epimer of α -spinasterol.



I. Chondrillasterol

The more soluble fraction obtained by the fractional recrystallization of the original benzoate mixture melted at 135° and 155° and showed $[\alpha]_D^{25} +23.5^\circ$. It was shown to be identical with cholestanyl benzoate by its conversion to cholestanol and cholestanyl acetate. It is estimated that the original sterol mixture contained about seventy per cent cholestanol and thirty per cent chondrillasterol.

EXPERIMENTAL

All melting points are corrected. All optical rotations were taken in a 1-dm. tube, the sample being dissolved in 3.06 cc. of chloroform.

Preparation of the sterol. The freshly collected sponges were first placed for several hours in sea water containing 5% of a commercial formalin solution and then air dried. The hard material was passed through a coarse meat grinder and thoroughly extracted with acetone in a large Soxhlet apparatus. After evaporation of the acetone, the extract, which contained considerable amount of water, was mixed with benzene, and the water was removed by co-distillation. Some smeary, brown, water-soluble material remained undissolved in benzene. The benzene extract was then evaporated to dryness, and the residue dried to constant weight *in vacuo* at 80°. It represented the acetone-benzene soluble material (Table I).

The sponge residue contained considerable quantities of inorganic impurities consisting essentially of calcium carbonate, such as coral sand shell fragments. In order to obtain reasonably accurate data on the fat content of the true sponge material and its organic fraction, a representative sample of the sponge, 3–10 g. was burnt and the ash determined. Another sample was boiled with concentrated nitric acid until all organic matter and the inorganic impurities had dissolved. The undissolved material consisted of the siliceous spicules of the sponge. They were washed with water, acetone, and ether, dried, and weighed. The difference between the percentages of ash and spicules represents the percentage of non-spicular ash. This ash may be regarded as of essentially extraneous origin. The figures shown in Table I are based on weights of crude sponge material from which the non-spicular ash has been subtracted.

The acetone-benzene soluble fraction of the sponge was a dark green, wax-like material. It was saponified, and the unsaponifiable matter isolated as previously described. The sterol content of an aliquot part of the unsaponifiable fraction was determined by the digitonin method. The bulk of the material was extracted with boiling methanol until all but a small amount of brown, resinous matter had dissolved. Upon cooling, the methanol solution deposited the sterol.

Chondrillasteryl benzoate. To a solution of one part by weight of the crude sterol in ten parts by volume of anhydrous pyridine was added about one part by weight of benzoyl chloride. The mixture was kept at 70° for twenty hours and then poured into a large volume of hot methanol. After cooling, the benzoate was collected and recrystallized from a mixture of ethanol and benzene; m.p. 135–170°, $[\alpha]_D^{25} +15^\circ$. Twelve recrystallizations of the crude benzoate from ethyl acetate, dioxane, and benzene-ethanol gave a product of constant melting point; m.p. 194–195°, $[\alpha]_D^{25} +4.0^\circ$, $[M]_D +21^\circ$ (53.6 mg., $\alpha +0.07^\circ$).

Anal. Calc'd for $C_{36}H_{52}O_2$: C, 83.66; H, 10.14.

Found: C, 83.57; H, 10.13.

Chondrillasterol. The benzoate described above was saponified with alcoholic potassium hydroxide in the presence of some ether. The sterol was recrystallized four times from ethanol, m.p. 168–169°, $[\alpha]_D^{25} -1.1^\circ$, $[M]_D -4^\circ$ (55.6 mg., $\alpha -0.02^\circ$). The sterol contains solvent of crystallization which is very difficult to remove.

Anal. Calc'd for $C_{28}H_{46}O$: C, 83.92; H, 12.08.

Found: C, 83.10; H, 12.10.

Chondrillasteryl acetate. The acetate was prepared by refluxing the sterol with acetic anhydride. It was recrystallized several times from absolute ethanol, a chloroform-methanol mixture, and ether, m.p. 175–176°, $[\alpha]_D^{25} -1^\circ$, $[M]_D -5^\circ$ (56.6 mg., $\alpha -0.01$ to -0.02°).

Anal. Calc'd for $C_{27}H_{46}O_2$: C, 81.88; H, 11.08.

Found: C, 81.43; H, 11.07.

α -Chondrillasterenyl acetate. A solution of chondrillasteryl acetate in glacial acetic acid was hydrogenated at room temperature with a platinum black catalyst. Absorption of hydrogen ceased after one mole had been consumed. The filtered solution was concentrated to a small volume and the acetate precipitated by the addition of methanol, m.p. 111–112°, $[\alpha]_D^{19} +8.9$, $[M]_D +41^\circ$ (44.5 mg., $\alpha +0.13^\circ$).

Anal. Calc'd for $C_{13}H_{22}O_2$: C, 81.52; H, 11.48.

Found: C, 81.55; H, 11.29.

Chondrillastanyl (poriferastanyl) acetate. A stream of dry hydrogen chloride was passed

for five hours through a cooled solution of 290 mg. of α -chondrillasteryl acetate in 10 cc. of chloroform. The volume was kept fairly constant by occasional additions of chloroform. The solution was then washed with dilute sodium carbonate solution and water, and dried over anhydrous sodium carbonate. It was evaporated to dryness, and the residue dissolved in acetic acid and hydrogenated at room temperature with a platinum black catalyst. The absorption of hydrogen ceased after somewhat less than one mole had been consumed. The filtered solution was then concentrated, the acetate collected and once more treated with hydrogen chloride and hydrogenated as described above. The final product, 150 mg., was recrystallized from methanol-chloroform, m.p. 139–140°, $[\alpha]_D^{25} +15^\circ$, $[M]_D +69^\circ$ (45.1 mg., $\alpha +0.22^\circ$). The acetate did not give a melting point depression when mixed with authentic poriferastanyl acetate.

Anal. Calc'd for $C_{41}H_{64}O_2$: C, 81.16; H, 11.87.

Found: C, 81.28; H, 12.05.

Chondrillastanol (poriferastanol). Saponification of the acetate described above gave the stanol, m.p. 142–143°, $[\alpha]_D^{25} +22.4^\circ$ (45.1 mg., $\alpha +0.33^\circ$). It did not give a melting point depression when mixed with authentic poriferastanol.

Ozonization of chondrillasteryl acetate. A sample was used which contained some cholestanyl acetate as an impurity. The ozonization was carried out as previously described (7) and the volatile aldehyde was isolated as the 2,4-dinitrophenylhydrazone. Several recrystallizations were required to raise the melting point to 115–116°, $[\alpha]_D^{25} +5.7^\circ$ (16.1 mg., $\alpha +0.03^\circ$). When mixed with the corresponding hydrazone from ethylisopropylacetaldehyde obtained from poriferasterol (m.p. 116–117°, $[\alpha]_D^{25} +4^\circ$) it melted at 115–117°.

Anal. Calc'd for $C_{41}H_{64}N_4O_4$: C, 53.05; H, 6.16.

$C_{42}H_{66}N_4O_4$: C, 51.42; H, 5.76

Found: C, 52.71; H, 6.12.

Cholestanyl benzoate. After several days there appeared in the first mother liquor from the recrystallization of chondrillasteryl benzoate some nicely crystalline material of uniform appearance. It was recrystallized several times from dioxane and benzene-ethanol, m.p. 135° (turbid liquid), 155° (clear); $[\alpha]_D^{25} +23.5^\circ$ (31.1 mg., $\alpha +0.23^\circ$). Hydrolysis of the benzoate gave cholestanol, m.p. 142°; $[\alpha]_D^{25} +23^\circ$ (21.3 mg., $\alpha +0.16^\circ$), and acetylation of the latter gave cholestanyl acetate, m.p. 111°; $[\alpha]_D^{25} +13^\circ$ (31.2 mg., $\alpha +0.13^\circ$). None of these compounds gave melting point depressions when mixed with authentic material.

SUMMARY

The sterols from the sponge, *Chondrilla nucula* Schmidt, have been isolated and investigated.

One of the sterols, the major component of the mixture, has been identified as cholestanol.

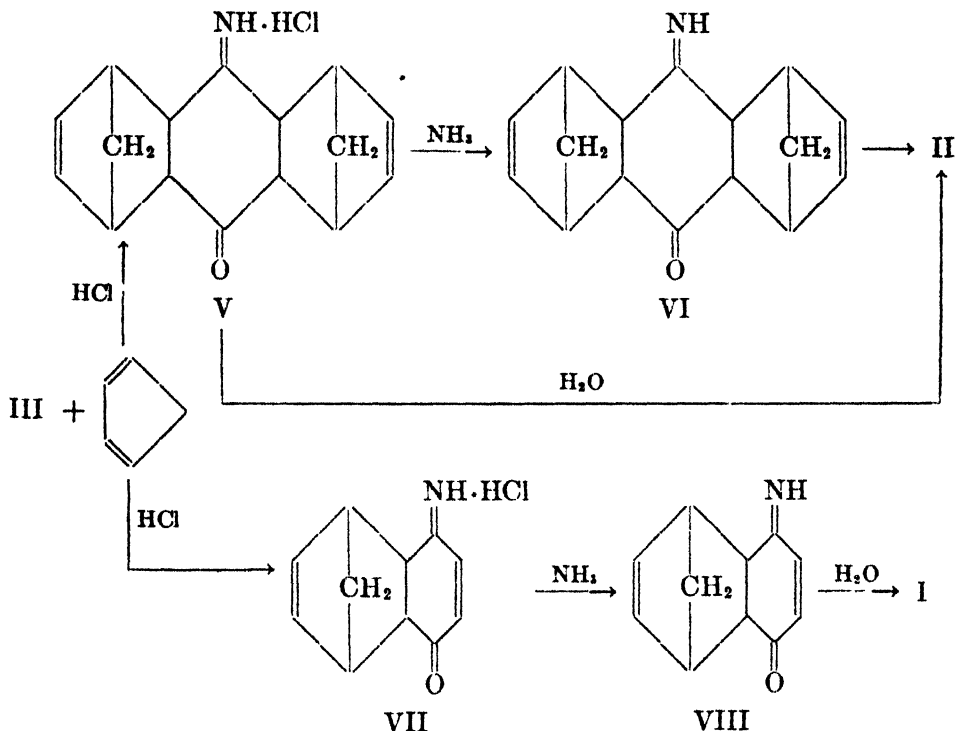
The second sterol, chondrillasterol, has been shown to be a new di-unsaturated compound, $C_{29}H_{48}O$. It has been demonstrated that it is the C_{24} -epimer of α -spinasterol.

NEW HAVEN, CONN.

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Quinonimine was prepared in ethereal solution by the silver oxide oxidation of *p*-aminophenol. Treated with an excess of cyclopentadiene, quinonimine does not react except to polymerize to a cokelike mass. When chloroacetic acid was added as a catalyst to a solution of quinonimine and cyclopentadiene in ether, a product resembling an indophenol was formed but there was no evidence of a Diels-Alder reaction having occurred. However, when concentrated hydrochloric acid was used as catalyst in place of chloroacetic acid, a rapid reaction took place between the cyclopentadiene and quinonimine (used in a molar ratio of 2.4:1) to yield a solid product (V) which, after crystallization from alcohol-ether, was a nearly colorless solid, melting with decomposition at 126–127°. Compound V possesses the general properties of an imine hydrochloride. It contains chlorine and is soluble in water and alcohol but is insoluble in ether. It was shown to be dicyclopentadienequinonimine hydrochloride by its ready hydrolysis to dicyclopentadienequinone (II), which was identified by its melting point and mixed melting point with an authentic sample of II. Compound V is stable and will stand without change for years.



Free dicyclopentadienequinonimine (VI) itself was obtained by treatment of a suspension of V in absolute ether with dry gaseous ammonia. It is a colorless solid, melting at 119–122°. Its identity was shown by carbon-hydrogen analyses and by hydrolysis with dilute sulfuric acid to give dicyclopentadienequinone and one mole of ammonia. Compound VI will stand without decomposition for months but eventually changes to a black tar.

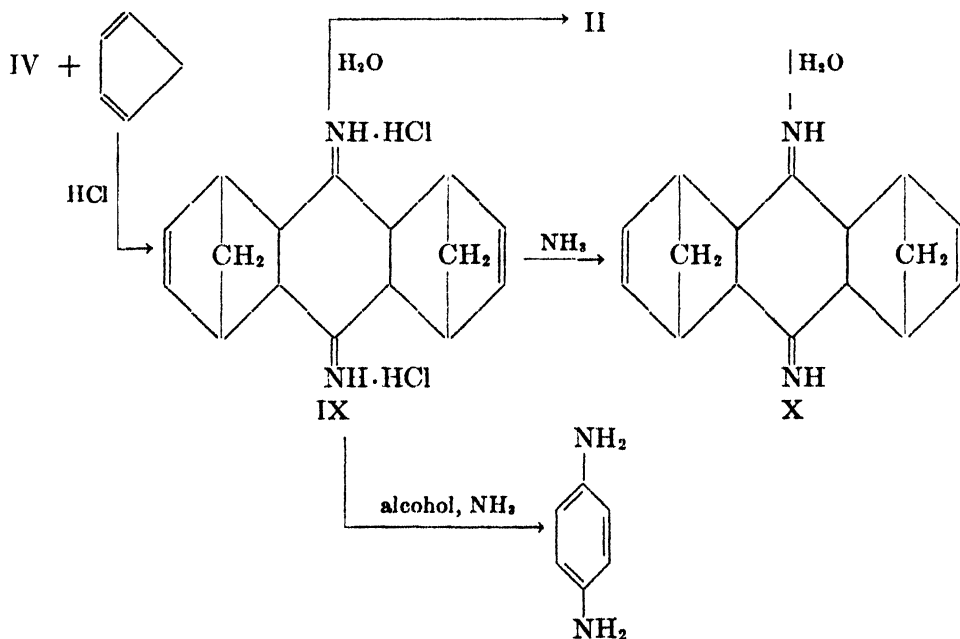
Attempts were made to isolate cyclopentadienequinonimine (VIII) from reac-

tion mixtures of quinonimine and cyclopentadiene. The results of these efforts, while not entirely conclusive, indicate that it was obtained. Cyclopentadiene and quinonimine (in a molar ratio of 1.19:1) reacted in the presence of hydrochloric acid to yield a mixture of two solids which could be separated by hand. One of these was V, the other consisted of greenish flakes, melting at 85°. It seems likely that this latter product was cyclopentadienequinonimine hydrochloride (VII). Unfortunately, attempts to repeat this run and thereby to obtain more of this material were not successful.

When equimolar amounts of cyclopentadiene and quinonimine reacted in the presence of hydrochloric acid, a greenish-black, partially crystalline mass was formed which was probable VII, mixed with tarry by-products. A light yellow solid, melting at 75–78°, was obtained when this greenish-black product was suspended in ether and treated with gaseous ammonia. That this light yellow solid was cyclopentadienequinonimine (VIII) is indicated by fairly good carbon and hydrogen analyses and by its hydrolysis to ammonia and to a white solid, melting at about 80°. Not enough of this white solid was obtained for a mixed melting point but it seems likely that it was cyclopentadienequinone (I) (m.p. 77–78°).

Previous work in this laboratory had shown that quinonediimine will not react with cyclopentadiene in ether solution, either with or without hydrogen chloride as catalyst, nor will these compounds react when ground together in a mortar. In all cases, only polymerization of the quinonediimine was observed.

However, in this study it was found that cyclopentadiene and quinonediimine react readily in ether solution in the presence of hydrochloric acid to yield an orange-red solid. This solid is believed to have been dicyclopentadienequinonediimine dihydrochloride (IX) since, upon standing with water, it gave a 67% yield of dicyclopentadienequinone.



Attempts to purify IX by solution in alcohol and reprecipitation with ether yielded *p*-phenylenediamine. It has been shown by Willstätter and Pfannenstiel (4) that the method of preparing quinonediimine used in this study gives solutions free from unoxidized *p*-phenylenediamine. It seems very likely that there was a reversion of the cyclopentadiene-quinonediimine adduct, during this attempted purification of IX, and that the quinonediimine thus formed was reduced by the alcohol present to *p*-phenylenediamine.

Compound IX was used for further work without purification. It was suspended in ether and treated with dry gaseous ammonia to yield a yellow solid which, after repeated crystallization from benzene and petroleum ether, melted at 110–120°. This yellow solid was shown to be dicyclopentadienequinonediimine (X) by its nitrogen analysis and by its hydrolysis to ammonia and dicyclopentadienequinone.

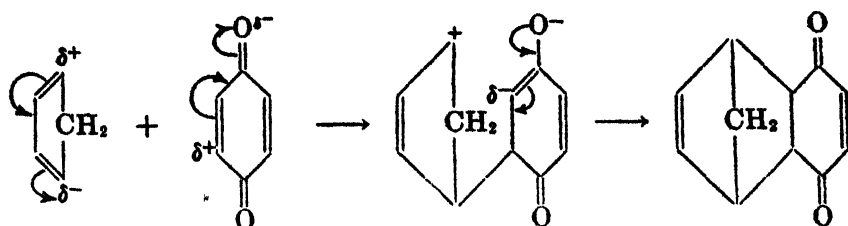
An attempt to prepare cyclopentadienequinonediimine by the reaction of equimolar amounts of cyclopentadiene and quinonediimine in the presence of hydrochloric acid gave a black solid. Treatment of this black solid yielded only *p*-phenylenediamine.

It was observed during this work that all of these imines were so reactive and unstable that, usually, only very low yields of the purified products could be obtained. In all of the hydrolyses of these imines to ammonia and the corresponding carbonyl compounds, side reactions occurred which held part of the nitrogen in non-hydrolyzable forms.

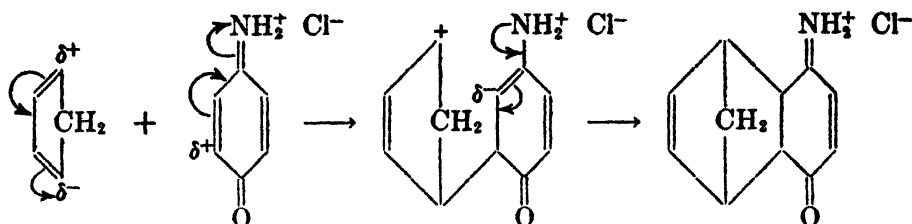
The catalytic effect of hydrochloric acid upon these reactions is of considerable interest. Wassermann (5) has reported a catalytic effect in the addition of cyclopentadiene to benzoquinone and other quinones; acidic substances, such as acetic acid, chloroacetic acid, bromoacetic acid, trichloroacetic acid, phenol and hydrochloric acid, produce a slight increase in the rate of reaction and pyridine produces a slight decrease. Trimethylamine, however, produces an increase. Fairclough and Hinshelwood (6) state that the reaction between cyclopentadiene and quinone takes place approximately five times as fast in highly polar solvents as in non-polar solvents. Despite these findings, however, the Diels-Alder reaction is not generally regarded as being susceptible to catalysis (7).

The work here reported has shown that, with the reaction of cyclopentadiene with quinonimine and quinonediimine, the presence of hydrochloric acid or, possibly, other highly acidic substances is necessary for the reaction to proceed at all. It remains to account for this effect. The following explanation is proposed.

The Diels-Alder reaction is regarded (7, 8) as the addition of a nucleophilic diene to the electrophilic center of the activated double bond system. This may be pictured with quinone and cyclopentadiene:



In quinonimine and quinonediimine, apparently, there exist no carbon atoms whose electrophilic character is great enough to cause reaction with cyclopentadiene. Upon addition of hydrochloric acid, however, the imine groups are converted to imonium groups and, it is suggested, the positive charge carried by these groups bring about electronic displacements which increase the electrophilic character of the carbon atoms adjacent to the carbonyl and imonium groups. The reaction between quinonimine and cyclopentadiene in the presence of hydrochloric acid can be written in the following manner:



Similar effects will produce an added reactivity on the part of quinonediimine. With this compound it is possible that either one or both of the imine groups may be converted to imonium groups; in either case, the electrophilic nature of the reactive carbon atoms in the molecule will be enhanced.

EXPERIMENTAL

Quinonimine and quinonediimine were prepared by the method of Willstätter and Pfannenstiel (4).

Preparation of dicyclopentadienequinonimine hydrochloride. A solution of quinonimine was prepared by the silver oxide oxidation of 3.0 g. (0.0275 mole) of *p*-aminophenol in 900 ml. of absolute ether. The dark yellow solution was slowly added, with a swirling motion, to a mixture of 5.5 ml. (4.4 g., 0.0666 mole) of freshly distilled cyclopentadiene, 25 ml. of 95% alcohol and 6 ml. of 12 *N* hydrochloric acid. The mixture became distinctly green at one stage of the addition. The mixture was allowed to stand for five hours in an ice-bath before being filtered. The yield of crude imine hydrochloride, a dark yellow crystalline solid, was 3.9 g. (52%). It was purified by dissolving in small portions in small volumes of 95% alcohol, filtering, and adding two volumes of ether, cooling, and filtering off the precipitated imine hydrochloride. It is a nearly colorless solid, melting with decomposition at 126–127°.

Preparation dicyclopentadienequinonimine. The imine was liberated from its hydrochloride by suspending small portions of the salt in ether, through which was passed dry ammonia gas. The ether solution of the imine was filtered and the free imine obtained by evaporation of the ether solution under reduced pressure. After one crystallization from ether it melted at 119–122°.

Anal. Calc'd for $C_{16}H_{17}NO$: C, 80.30; H, 7.15.

Found: C, 79.86; H, 7.06.

The quantitative hydrolysis of the imine was brought about by dissolving a weighed sample of the imine in standard dilute sulfuric acid. The solution was kept at 0° for nine days, then filtered. After another 24 hours no further precipitate had appeared and the solution was warmed on a steam-bath to ensure complete hydrolysis. It was then titrated to a phenolphthalein end-point with standard dilute sodium hydroxide solution. The ammonia obtained was 86% of theoretical. The solid product filtered off during this hydrolysis melted at 156–158°. The mixed melting point of this substance with a known sample of dicyclopentadienequinone was 156–158°.

It was observed that attempts to effect this hydrolysis at higher temperatures or with the use of hydrochloric acid instead of sulfuric acid gave lower yields of ammonia.

Preparation of cyclopentadienequinonimine. A solution of quinonimine was prepared by the oxidation of 1.0 g. (0.0092 mole) of *p*-aminophenol in 300 ml. of absolute ether. It was added with swirling to a mixture of 0.9 ml. (0.72 g., 0.0110 mole) of freshly distilled cyclopentadiene, 25 ml. of 95% alcohol, and 2 ml. of 12 *N* hydrochloric acid, held at 0°. The mixture darkened rapidly. After standing for several hours at 0°, the mixture was filtered to yield a mixture of small yellowish-brown nodules and greenish flakes. The yellowish-brown substances melted with decomposition at 126–127°. The other material, the greenish flakes, melted with decomposition at 85°. It is believed that these greenish flakes were composed of cyclopentadienequinonimine hydrochloride in fairly pure form. Attempts to repeat this experiment were not successful.

In other experiments, solutions of quinonimine prepared by the oxidation of 1.0 g. (0.0092 mole) of *p*-aminophenol were added to mixtures of 0.85 ml. (0.68 g., 0.0104 mole) of cyclopentadiene, 2 ml. of 12 *N* hydrochloric acid, and 25 ml. of alcohol. The products consisted of a greenish-black, partially crystalline material with a melting point of wide range.

This greenish-black material was suspended in ether and treated with dry ammonia gas. After filtration, the ether solution was concentrated under reduced pressure until a resinous material separated. The remaining solution was drained off and the resinous material subjected to reduced pressure. Under this treatment it rapidly puffed up to a spongy yellow solid melting at 75–78°.

Anal. Calc'd for $C_{11}H_{11}NO$: C, 76.27; H, 6.41.

Found: C, 77.29; H, 6.72.

A quantitative hydrolysis of this free imine was attempted. A weighed sample was dissolved in dilute sulfuric acid. The solution was kept at 0°, filtered, and warmed on a steam-bath. It was then made alkaline with sodium hydroxide and the ammonia was distilled into standard hydrochloric acid, which was then titrated to a phenolphthalein end-point. The amount of ammonia obtained was 16% of theoretical. A small amount of white substance was filtered from the hydrolysis mixture before distillation. It was found to melt at 80°. Not enough was available for a mixed melting point with known cyclopentadienequinone.

Preparation of dicyclopentadienequinonediimine dihydrochloride. A solution of quinonediimine, prepared by the oxidation of 1.0 g. (0.0092 mole) of *p*-phenylenediamine in 500 ml. of absolute ether, was added at 0° to a mixture of 5.3 ml. (4.3 g., 0.065 mole) of freshly distilled cyclopentadiene, 2 ml. of 12 *N* hydrochloric acid, and 30 ml. of 95% alcohol. A light tan flocculent precipitate was formed immediately but gradually settled to the bottom of the vessel in a semi-solid mass. Upon standing for an hour in an ice-bath, the semi-solid mass gradually crystallized and became orange-red in color. It was filtered off and washed with acetone and ether. The yield of crude imine hydrochloride was 0.93 g. (32%).

The hydrolysis of the crude imine hydrochloride to dicyclopentadienequinone was done as follows: 0.233 g. of the imine hydrochloride was dissolved in 25 ml. of water and the solution was allowed to stand for three days, then was filtered to give 0.12 g. of dicyclopentadienequinone (67%). After one crystallization from 50% alcohol, it melted at 153°.

The attempted purification of this imine hydrochloride was carried out as follows. Approximately 0.5 g. of the hydrochloride was dissolved in 150 ml. of 95% alcohol. The light brown solution was treated with 1.5 g. of decolorizing charcoal and filtered into 400 ml. of ether. The nearly colorless solid thus formed was filtered off and washed with ether. It was then suspended in 50 ml. of absolute ether and treated with dry ammonia gas. The resulting ether solution was filtered and evaporated to dryness, leaving a tan solid as residue. Recrystallization of this residue from benzene gave a light pink solid, melting at 140°. A mixed melting point with *p*-phenylenediamine gave no depression.

Preparation of dicyclopentadienequinonediimine. Approximately 0.8 g. of crude dicyclopentadienequinonediimine dihydrochloride was suspended in 30 ml. of absolute ether and treated with dry ammonia gas. The ether solution was then filtered and evaporated under

reduced pressure, giving the crude free imine. Five milliliters of dry benzene was added to this material, which dissolved completely but then began to deposit a tan solid which was filtered off (m.p. 238–239°). The filtrate was poured into 50 ml. of petroleum ether (b.p. 30–60°). A yellow solid, melting at 90–100°, was precipitated. This yellow solid was again dissolved in benzene and the solution again poured into petroleum ether. This treatment gave a light yellow solid, melting gradually between 110° and 120°. Further repetition of this method of purification failed to give a sharper or higher melting point and the use of other solvents was no more effective.

Anal. Calc'd for $C_{10}H_{12}N_2$: N, 11.76. Found: N, 11.73.

Hydrolysis of this imine to dicyclopentadienequinone was done as follows: 0.384 g. of the imine was dissolved in a mixture of 25 ml. of water and 0.5 ml. of 12 *N* hydrochloric acid. The solution was allowed to stand for two days; the dicyclopentadienequinone formed was then filtered off. The yield was 0.064 g. (17%).

Attempted preparation of cyclopentadienequinonediimine. Quinonediimine was prepared by the oxidation of 0.5 g. (0.0046 mole) of *p*-phenylenediamine in 150 ml. of absolute ether. The ether solution was added rapidly and with a swirling motion to a mixture of 0.75 ml. (0.6 g., 0.0091 mole) of cyclopentadiene, 1.5 ml. of 12 *N* hydrochloric acid and 9 ml. of 95% alcohol. A gray precipitate formed immediately. This precipitate darkened rapidly and turned to a sticky resin which, after standing for two hours, solidified somewhat. The solid was filtered and washed with ether. An attempt to hydrolyze this solid to cyclopentadienequinone by dissolving a portion of it in water gave only a very small amount of dark solid.

Another portion of the solid was suspended in ether and treated with dry ammonia gas. The solution resulting from this treatment was treated with decolorizing charcoal and filtered. Evaporation of the ether left a sticky solid which was recrystallized from benzene to give a brownish solid melting at 130–132°. A mixture of this solid with known *p*-phenylenediamine melted at 132–134°. Apparently the major reaction was a reduction of the quinonediimine rather than any appreciable amount of addition to the cyclopentadiene.

SUMMARY

It has been shown that cyclopentadiene will undergo the Diels-Alder reaction with quinonimine and with quinonediimine when hydrochloric acid is present in the reaction mixtures. In the absence of hydrochloric acid, the only reactions which occur appear to be polymerization of the imines.

An explanation has been proposed for the catalytic effect of hydrochloric acid.

FARGO, NORTH DAKOTA

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY¹]

n-ALKYL *beta*-HYDROXYPROPIONATES AND *beta*-ACETOXYPROPIONATES

M. L. FEIN AND C. H. FISHER

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Several derivatives of hydracrylic acid or *beta*-hydroxypropionic acid, needed in connection with other research, were prepared² from readily available starting materials by methods apparently more convenient than those hitherto described (1-5). The preparations of these products, several of which are new, and certain of their physical constants are reported here.

The ethyl, *n*-propyl, *n*-butyl, and *n*-octyl hydracrylates were prepared by passing dry HCl through ether solutions of ethylene cyanohydrin and the appropriate alcohols.³ The butyl and octyl esters were obtained in approximately 70% yields. The ethyl and propyl esters, which were more difficult to isolate because of their solubility in water, were obtained in lower yields. There was little tendency for the corresponding *beta*-chloropropionates to form under the conditions usually employed, but in one experiment both ethyl hydracrylate and ethyl *beta*-chloropropionate were formed when the reaction mixture was allowed to stand for about 10 days at room temperature.

The butyl ester of dimeric hydracrylic acid, $\text{HOCH}_2\text{CH}_2\text{COOCH}_2\text{CH}_2\text{COO}-\text{C}_4\text{H}_9$, was isolated as a by-product in the preparation of butyl hydracrylate (Table I). Possibly the dimer ester was formed by self-alcoholysis of butyl hydracrylate^{4, 5} or by the reaction of butanol with $\text{HOCH}_2\text{CH}_2\text{COOCH}_2\text{CH}_2\text{CN}$.

Ethyl and *n*-butyl hydracrylates were made also by saponification of ethylene cyanohydrin (10), acidification of the resulting sodium hydracrylate, and esterification of the free acid. This method resembled that described above in that it was less suitable for the preparation of the water-soluble ethyl hydracrylate.

The acetyl derivatives of the *n*-alkyl hydracrylates (Table I) were obtained in approximately 90% yields by acetylation with acetic anhydride. The propionate of methyl hydracrylate had been prepared by earlier workers (3) by acylation with propionyl chloride.

Physical constants. The boiling points given by Drushel and Holden (5) for the ethyl (84°, 12 mm.; 91.5°, 19 mm.; 95.5°, 22 mm.) and *n*-propyl, (102°, 19

¹ One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture.

² The preparation of hydracrylic esters prior to 1915 has been reviewed by Drushel (4, 5). The interesting synthesis of hydracrylic esters from propiolactone and alcohols was described (6) after the completion of the present work.

³ Earlier workers prepared related hydracrylic acid derivatives, that is, $\text{C}_2\text{H}_5\text{OCOCH}_2\cdot\text{CH}_2\text{COOC}_2\text{H}_5$ (7) and $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{OCH}_2\text{CH}_2\text{COOC}_2\text{H}_5$ (8), similarly from 2-cyanoethyl ethyl carbonate and 2-cyanoethyl toluenesulfonate, respectively.

⁴ The production of various esters of polymeric hydracrylic acid from β -propiolactone has been described (6).

⁵ Esters of polymeric lactic acid have been made by the self-alcoholysis of several alkyl lactates (9).

TABLE I
DERIVATIVES OF HYDRACRYLIC ACID AND 3-CHLOROPROPIONIC ACID^a

COMPOUND	B.P. °C (10 MM.)	n_D^{20}	d_4^{20}	MOLECULAR REFRACTION		SAPONIFICATION EQUIV.		CARBON, %		HYDROGEN, %	
				Calc'd	Obs.	Calc'd	Obs.	Calc'd	Obs.	Calc'd	Obs.
Methyl hydraerylate ^b	70	1.4228	1.1160	23.85	23.74	—	—	—	—	—	—
Ethyl "	76	1.4222	1.0589	28.47	28.36	118.1	118.9	50.83	50.87	8.53	8.41
n-Propyl "	89	1.4263	1.0243	33.09	33.08	132.2	131.6	54.52	54.62	9.15	9.02
n-Butyl "	101	1.4292	1.0006	37.70	37.67	146.2	146.6	57.51	57.36	9.59	9.40
n-Octyl "	150	1.4405	0.9488	56.18	56.24	202.3	202.1	65.31	65.36	10.96	11.02
Methyl beta-acetoxypionate	81	1.4169	1.1100	33.32	33.10	73.1	73.4	49.3	49.6	6.9	7.2
Ethyl "	88	1.4170	1.0651	37.83	37.81	80.1	80.8	52.49	52.65	7.55	7.82
n-Propyl "	99	1.4198	1.0382	42.45	42.44	87.1	87.2	55.16	55.10	8.10	8.02
n-Butyl "	111	1.4230	1.0179	47.07	47.09	94.1	93.9	57.42	57.64	8.57	8.88
n-Octyl "	159	1.4337	0.9684	65.54	65.64	122.2	122.3	63.90	63.74	9.90	9.86
n-Bu ester of dimeric hydraerylic acid ^c	157 (5 mm.)	1.4432	1.0874	53.31	53.23	109.12	109.0	55.03	55.10	8.31	8.61
Ethyl 3-chloropropionate ^d	60 (15 mm.)	1.4256	1.1035	31.82	31.69	—	—	43.97	44.11	6.64	7.01
" "	60 (15 mm.)	1.4240	1.0962	—	—	—	—	43.97	44.14	6.64	6.79

^a After this manuscript had been completed, samples of methyl, ethyl, n-propyl, and n-butyl hydraerylates generously supplied by J. E. Jansen and T. L. Gresham of the B. F. Goodrich Company were redistilled and their physical properties determined: the resulting physical properties of the ethyl, propyl, and butyl esters were in excellent agreement with those given in Table I.

^b Constants obtained with sample supplied by J. E. Jansen and T. L. Gresham after redistillation.

^c Hydroxyl groups: theoretical, 7.86%; found, 7.1%.

^d From 3-chloropropionyl chloride and ethanol; observed chlorine content, 25.74% (theoretical, 25.96%).

^e This compound and ethyl hydraerylate were obtained from ethylene cyanohydrin, ethanol, and hydrogen chloride.

mm.; 120°, 43 mm.) esters of hydracrylic acid are in fair agreement with those observed (Fig. 1 and Tables I and II) in the present work. The hydracrylates

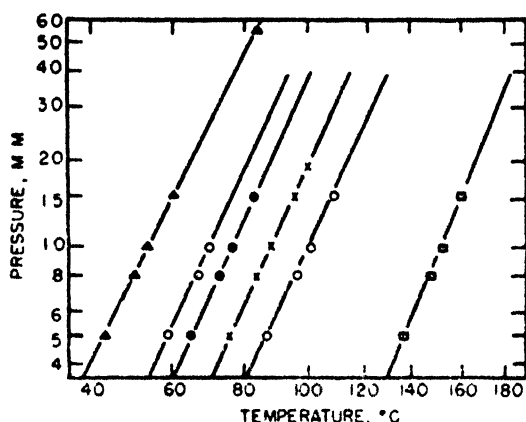


FIG. 1. BOILING POINT OF *n*-ALKYL HYDRACRYLATES AND ETHYL 3-CHLOROPROPIONATE (Et Chloropropionate, \blacktriangle Hydracrylates: Me— \circ ; Et— \bullet ; Pr— \times ; Bu— \square ; Octyl— \square .)

TABLE II
BOILING POINTS AND VISCOSITIES OF HYDRACRYLIC ESTERS^{a, b}

COMPOUND	BOILING POINT		VISCOSITY (20°)		POISES $\times 10^6$ /MOL. VOL.
	°C.	Mm.	Centistokes	Centipoises	
Ethyl hydracrylate	187	754	4.196	4.443	398.26
<i>n</i> -Propyl "	202	760	5.193	5.319	412.26
<i>n</i> -Butyl "	216-218	754	6.208	6.212	425.22
<i>n</i> -Octyl "	276	755	13.076	12.406	581.87
Ethyl <i>beta</i> -acetoxypropionate	201	755	2.606	2.776	184.60
<i>n</i> -Propyl "	215	758	2.966	3.079	183.51
<i>n</i> -Butyl "	231	756	3.365	3.425	185.22
<i>n</i> -Octyl "	284	755	6.554	6.347	251.58

^a Distillation of the *n*-alkyl hydracrylates at atmospheric pressure caused some decomposition.

^b Dunstan and co-workers (References 15 and 16) observed the value for $\frac{\text{poises} \times 10^6}{\text{mol. vol.}}$, which is under 100 for simple esters, ketones, and alkyl halides, is relatively large for highly associated compounds. Examples are: Water, 500; phenol, 453; glycol, 2750; formic acid, 415; and formamide, 682. The values for the ethyl ethers of ethyl, propyl, butyl, and octyl hydracrylates are, respectively, 82, 86, 89, and 135 (Ref. 17).

and *beta*-acetoxypropionates boiled considerably higher than the corresponding isomeric lactates and *alpha*-acetoxypropionates (Figs. 2 and 3).

Methyl and ethyl hydracrylate resembled *n*-alkanols of comparable molecular weight in that they boiled about 14° lower than their acetyl derivatives (Table

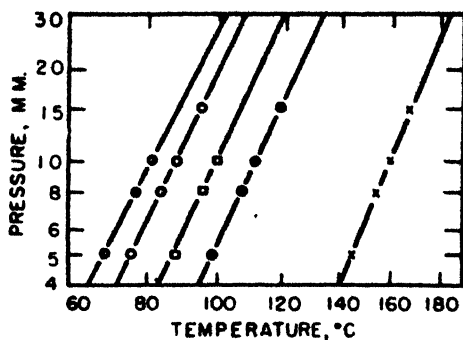
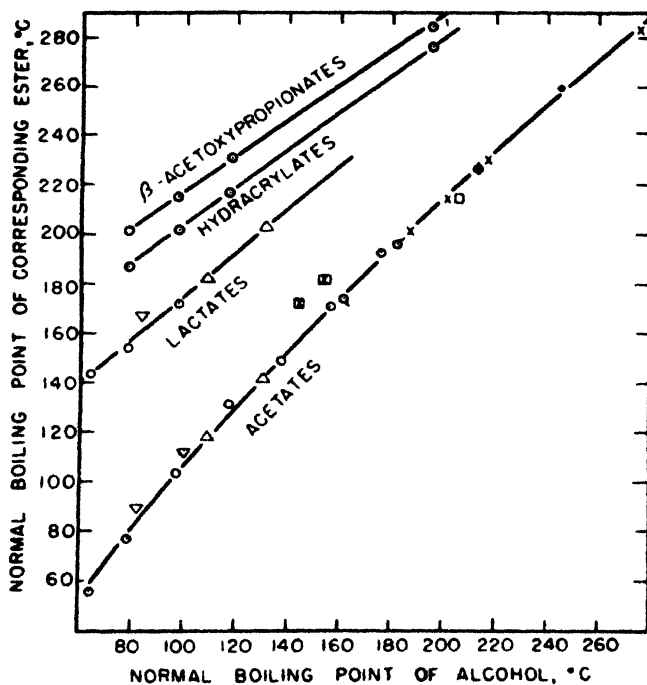


FIG. 2. BOILING POINTS OF *n*-ALKYL β -ACETOXYPROPIONATES
(\odot —Methyl; \circ —Ethyl; \square —Propyl; \bullet —Butyl; \times —Octyl)

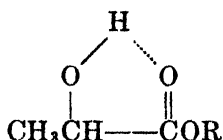


- | | |
|--|---|
| \circ — <i>n</i> -ALKYL | \bigcirc —CYCLOHEXYL |
| Δ —BRANCHED-ALKYL | σ —Ph |
| ∇ —SEC-ALKYL | \square —PhCH ₂ |
| ϕ —BORNYL | \bullet —PhOCH ₂ CH ₂ |
| \times —CH ₂ CH ₂ COOR | \boxtimes —CH(CH ₃)COOR |

FIG. 3. RELATION OF BOILING POINT OF ALCOHOL TO THAT OF THE CORRESPONDING
ESTER

- | | |
|--|---|
| \odot — <i>n</i> -Alkyl | \bigcirc —Cyclohexyl |
| Δ —Branched—Alkyl | σ —Ph |
| ∇ —Sec.—Alkyl | \square —PhCH ₂ |
| ϕ —Bornyl | \bullet —PhOCH ₂ CH ₂ |
| \times —CH ₂ CH ₂ COOR | \boxtimes —CH(CH ₃)COOR |

II and Fig. 3). The isomeric methyl and ethyl lactates, which (11) exist largely as



have boiling points about 28° lower⁶ than their corresponding acetyl derivatives (14).

As is true with many other homologous series (17-20), the square of the absolute boiling points of the *n*-alkyl hydracrylates and *beta*-acetoxypropionates was a straight line function of the number of carbon atoms. The equations below express the relation between boiling point (T = b.p., °K.) and carbon atoms (x):

$$\text{Hydracrylates, 760 mm. : } T^2 10^{-4} = 1.50x + 13.64$$

$$10 \text{ mm. : } T^2 10^{-4} = 0.96x + 7.32$$

$$\text{Acetoxypropionates, 760 mm. : } T^2 10^{-4} = 1.42x + 12.56$$

$$10 \text{ mm. : } T^2 10^{-4} = 0.96x + 6.16$$

Since the hydracrylates could be distilled at atmospheric pressure without serious decomposition, apparently the tendency of these esters to dehydrate on heating is less than that of certain more complex *beta*-hydroxy esters (21).

The density (d_4^{20}) and refractive index (n_D^{20}) of the *n*-alkyl hydracrylates of Table I are related to the total number of carbon atoms (x), as shown by the equations:⁷

$$x/d = 1.147x - 1.026$$

$$x/n = 0.686x + 0.093$$

The *n*-alkyl hydracrylates, less viscous than the *n*-alkanols of equal molecular weight, are more viscous than the *beta*-acetoxypropionates, *beta*-ethoxypropionates (Fig. 4), and the isomeric *n*-alkyl lactates (22). Because of their relatively high viscosities and boiling points, it seems likely that the hydracrylates are more associated than the corresponding lactates; this conclusion is in harmony with the generalization of Bingham and Spooner (22) that primary alcohols are more highly associated than the isomeric secondary alcohols.

In harmony with their view are the high viscosity-molecular volume values of the *n*-alkyl hydracrylates (Table II). As would be expected, the acetyl and

⁶ Certain other hydroxy compounds structurally capable of existence in the chelate form also have boiling points (12) considerably lower than those of the corresponding acetates. For example, *o*-nitrophenol (b.p. 214.5°) and eugenol (b.p. 253.5°) boil 37° and 27° lower than their corresponding acetates. Acetoin (b.p. 143°) has a boiling point 28° lower than that of its acetate (13).

⁷ The calculated refractive index of ethyl hydracrylate, agreeing poorly with the experimental value, is an exception.

ethyl ether derivatives have much lower values than the corresponding alkyl hydracrylates (Table II).

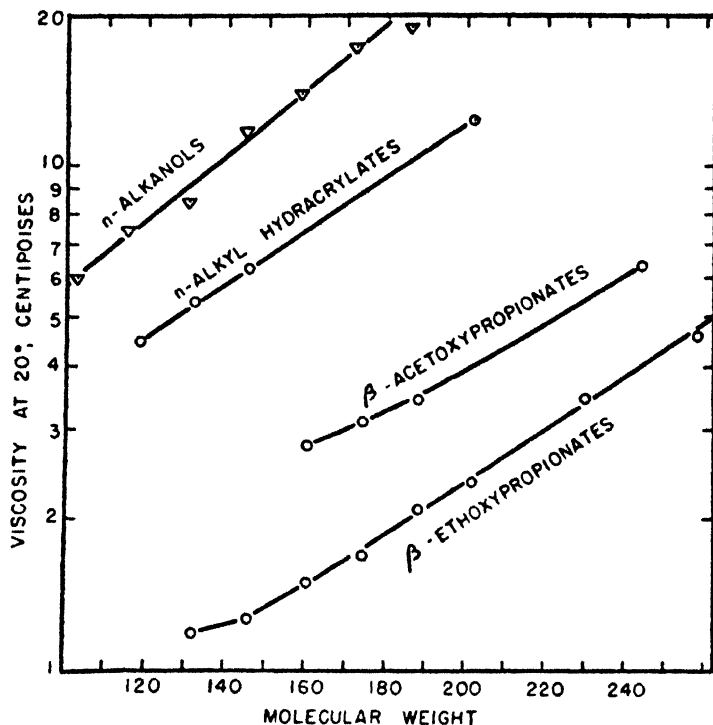


FIG. 4. VISCOSITY OF *n*-ALKANOLS AND DERIVATIVES OF HYDRACRYLIC ACID

ACKNOWLEDGMENT

The authors are grateful to Mildred S. Gasper, Ruth W. Brand, and C. O. Willits for the determination of carbon and hydrogen and saponification equivalents.

EXPERIMENTAL

n-Butyl hydracrylate and 2-carbobutoxyethyl hydracrylate. Dry hydrogen chloride was passed into a mixture of 2 moles of ethylene cyanohydrin, 4 moles of *n*-butanol, and 200 ml. of ethyl ether contained in a 1-liter three-neck flask immersed in ice-water and fitted with a mechanical stirrer.

After the mixture had been saturated with hydrogen chloride, the flask was placed in a refrigerator for two days. During this period a mass of crystals formed. The flask was then attached to a vacuum line (water aspirator) to remove excess hydrogen chloride; this operation was occasionally interrupted so that dry air could be blown through the flask. Benzene (200 ml.) was added, and the mixture was stirred. About 200 ml. of water was then added slowly. The water layer was separated and washed with benzene. The combined benzene solution was washed with water and sodium bicarbonate solution. The benzene-water azeotrope and excess butanol were distilled under water-pump vacuum; the butyl hydracrylate distilled at about 0.1 mm. (The yield was 70%.) The *n*-butyl ester was much less soluble in water (approximately 0.75 g. per 100 ml.) than the isobutyl ester [given as 1 part in 18 by Drushel and Holden (5)].

The distillation residue from one of the butyl hydracrylate preparations was distilled further, yielding a product (Table I) believed, on the basis of its analysis, to be the butyl ester of dimeric hydracrylic acid.

n-Propyl hydracrylate. (A) When prepared by the method described above for the *n*-butyl ester, but with *n*-propanol instead of *n*-butanol, the yield was 36%.

(B) The following modification was preferable: Approximately 80 g. of dry hydrogen chloride was passed into ether maintained at 10 to 20°. First, *n*-propanol (240 g., 4 moles) and then 142 g. (2 moles) of ethylene cyanohydrin were added (with stirring) to the ether solution. The flask was then allowed to stand at room temperature until the temperature of the contents rose to 40°. After standing for several days, the flask contained an almost solid mass of crystals. By using essentially the isolation procedure described for the *n*-butyl ester, *n*-propyl hydracrylate was obtained from the reaction mixture in 58% yield.

In agreement with Drushel and Holden (5), the *n*-propyl ester was observed to be miscible with water.

Ethyl hydracrylate and a fraction that appeared to be impure ethyl *beta*-chloropropionate (Table I) were obtained from ethanol and ethylene cyanohydrin, with the modified (B) propyl hydracrylate procedure. Even after repeated fractional distillations, the constants of the fraction assumed to consist largely of ethyl *beta*-chloropropionate were not identical with those observed with an authentic specimen prepared from ethanol and *beta*-chloropropionyl chloride (Table I). Curtius and Müller (23) also were unable to purify completely ethyl *beta*-chloropropionate obtained as a by-product in the preparation of ethyl hydracrylate.

n-Alkyl *beta*-acetoxypropionates. Acetic anhydride was added slowly to the alkyl hydracrylates (0.5 mole each), one drop of concentrated sulfuric acid or ten drops of acetyl chloride being used as catalyst. After the reaction appeared to be essentially complete, the mixture was warmed on a steam-bath for about one hour. Sodium acetate was added to neutralize the catalyst. The mixture was filtered, and the filtrate was distilled under reduced pressure. Approximately 90% yields of the acetyl derivatives were obtained.

Physical constants. The products were redistilled through 50-cm. Vigreux columns, and middle, narrow-boiling fractions were used for the determination of constants (Tables I and II). Boiling points at about 10 mm. (Fig. 1 and 2) were determined by careful distillation through a similar column, the pressure being read from a Dubrovin gauge (24). The boiling points at atmospheric pressure were less accurate because of some decomposition, but they were only about 4° lower than those calculated by the equation, given below (B_{10} = b.p. at 10 mm.), derived from boiling points of the *n*-alkyl *beta*-ethoxypropionates (17).

$$\text{b.p. at 760 mm.} = \frac{\text{b.p.}_{10} + 84}{0.834}$$

Refractive indices, densities, and viscosities were measured with an Abbé-type refractometer, a 25-ml. Leach pycnometer fitted with a thermometer (similar to 50 ml. size recommended by A.S.T.M. designation D153), and modified Ostwald pipettes that had been calibrated with samples of standard oils furnished by the National Bureau of Standards. The temperature of the baths used in these determinations was controlled within $\pm 0.05^\circ$. Control of pressure at 5.0, 8.0, 10.0, and 15.0 mm. for the data shown in Figs. 1 and 2 was achieved by use of a new-type pressure regulator which allows precise selection and close control of any desired pressure.*

Water solubility was determined by a modification of the method of Fordyce and Meyer (25), 50 ml. of water being used instead of 1 liter. The viscosities reported by Müller (26) for the *n*-alkanols were used in the construction of Fig. 4.

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* A description of this apparatus has not yet been published.

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[CONTRIBUTION FROM THE FERMENTATION DIVISION, NORTHERN REGIONAL RESEARCH
LABORATORY¹]

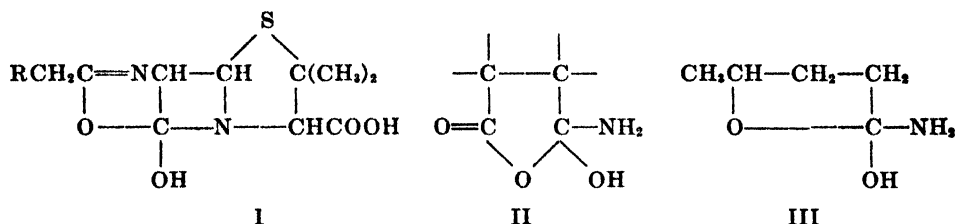
THE ACTION OF HYDRAZINE HYDRATE ON OXAZOLONES

FRANK H. STODOLA

Received June 1, 1948

During the early work on the penicillins, structure I was considered as a possibility for this class of compounds. A search of the literature for reference to substances having the grouping $\text{—O—C—N}<$ disclosed that as early as 1890

Anschütz (1) had assigned structures II and III to the reaction products of ammonia with anhydrides and lactones. The easy loss of



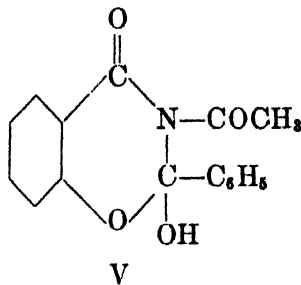
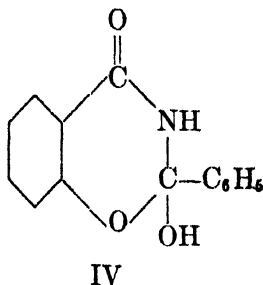
ammonia on heating was considered to be better explained by these structures

than by the simple amide (—C(=O)—NH_2) formulations used up to that time.

In 1898, Cramer (2) considered the Anschütz type of formula for the product obtained by the action of ammonia on the lactone of *o*-hydroxyphenylacetic acid but rejected it in favor of the ordinary amide structure. Two years later, Wedel (3) came to the same conclusion after a study of the action of hydrazine hydrate on the same lactone. In 1903, however, Meyer and Maier (4) revived the Anschütz formulation as a means of explaining the properties of the addition product of *o*-phenylenediamine and succinic anhydride. Likewise Blaise and Luttringer (5) in 1905 assigned the Anschütz structure to the reaction products of hydrazine hydrate with aliphatic lactones. These compounds were given the name "hydrazinolactones." The lability of the hydrazine with sulfuric acid and the formation of benzalazine with benzaldehyde were offered as evidence for the structure proposed.

In 1905–6, Titherley and co-workers (6, 7) attempted to explain some anomalies in the behavior of the benzoyl derivatives of salicylamide by means of formulations IV and V.

¹ One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.



These structures, however, were considered by Auwers (8, 9) as unlikely for stable compounds although he conceded the possibility of their existence as intermediates in rearrangements (10).

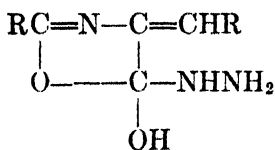
In 1928, Anschütz (11), in a summary of his work on the addition products of ammonia and anhydrides, re-affirmed his belief in the —O—C—N— structure,



particularly for compounds resulting from the addition of amines to substituted maleic anhydrides.

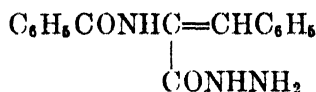
Darapsky, Berger, and Neuhaus (12) in 1936 re-opened the problem of the action of hydrazine hydrate on lactones and advanced good evidence in favor of the ordinary amide structure for the products.

The most recent advocates of the Anschütz formulation have been Vanghelovici and Stephanescu (13) who claim that hydrazine hydrate adds to oxazolones to give compounds of type VI. We were interested in these structures for, if they could have been shown at that time to be correct,



VI

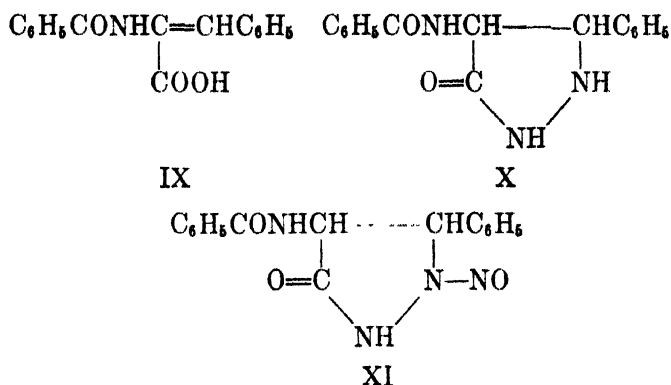
VII R = phenyl



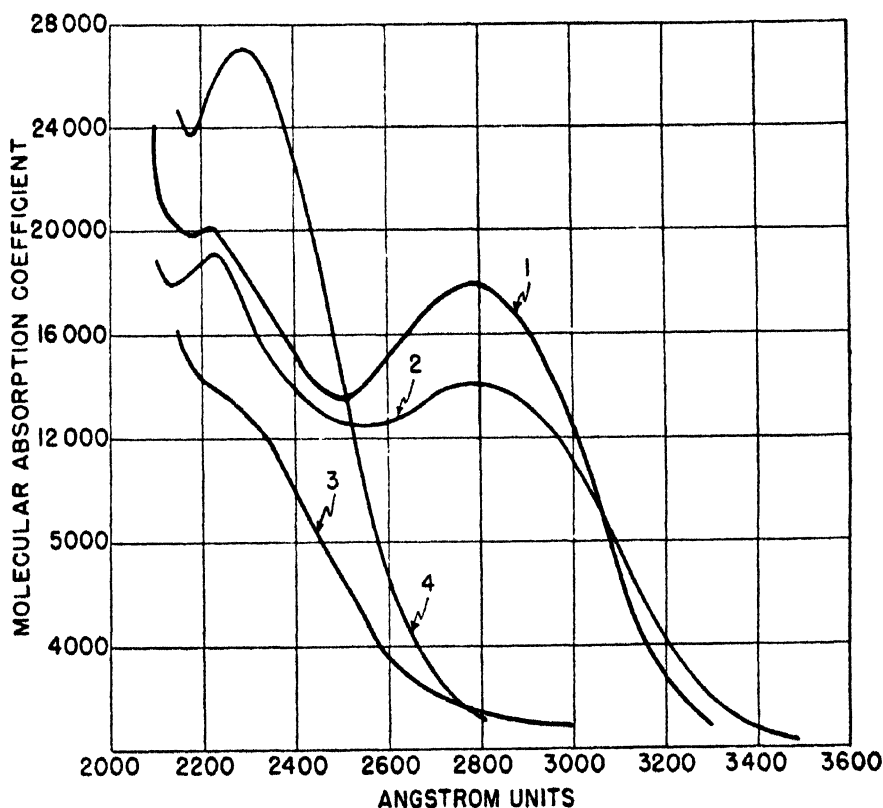
VIII

such hydrazine-oxazolone addition compounds would have been useful as models for penicillin structure studies.

Accordingly we repeated and extended the work of Vanghelovici and Stephanescu; we found, however, no evidence for the Anschütz type of structure. Instead, we have been able to show that the compound of m.p. 153°, to which the formula VII was assigned by the Roumanian workers, is the normal hydrazide VIII. Our evidence is based on the ultraviolet absorption spectrum of the compound. The absorption curve (curve 1; figure 1) shows a peak at 2800 Å, as does the acid IX (curve 2; figure 1). This peak is at a considerably shorter wavelength than would be expected for the system $\text{C}_6\text{H}_5\text{C=N—C=CHC}_6\text{H}_5$.



The azide formation and the reaction with aldehydes which were observed by Vanghelovici and Stephanescu are in agreement with hydrazide structure.



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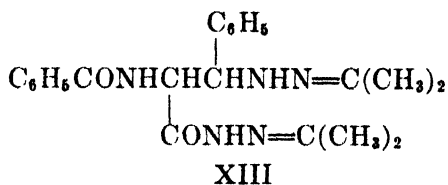
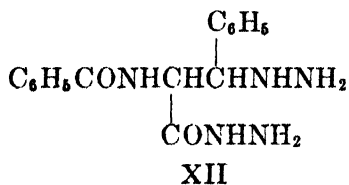
FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA

- (Curve 1. α -Benzoylamino-cinnamic acid hydrazide (VIII)
 Curve 2. α -Benzoylamino-cinnamic acid (IX) (8.736 mg. per liter)
 (Curve 3. 3-Phenyl-4-benzoylamino-5-pyrazolidone (X)
 (Curve 4. Diacetone derivative (XIII)

We have further been able to show that the compound of m.p. 229°, which Vanghelovici and Stephanescu assumed to be the normal hydrazide, is in reality the pyrazolidone X. It has already been observed by Knorr and Duden (14) that crotonic acid and phenylhydrazine react to form 1-phenyl-3-methyl-5-pyrazolidone. Rothenburg (15) has reported the preparation of pyrazolidone itself by the action of hydrazine hydrate on acrylic acid. The pyrazolidone formula here proposed is in accord with the absorption spectrum (curve 3; figure 1) which shows the disappearance of the peak at 2800 Å characteristic of the α,β -unsaturated acids. The inability of the compound to condense with aldehydes, and the formation of an acetyl derivative, are consistent with the the pyrazolidone structure. The claim of Vanghelovici and Stephanescu that they have formed an azide of this compound appears to be in error. We have succeeded in preparing the expected nitroso derivative XI which shows the properties to be anticipated on the basis of the work of Knorr and Duden (16), Muckermann (17), and Darapsky *et al.* (12).

An attempt was made to prepare the normal hydrazide by the action of hydrazine on the methyl ester of IX in methanol at room temperature. The crystalline product which separated, however, appeared to be XII since on treatment with acetone it yielded a compound analyzing as XIII, the absorption spectrum (curve 4; figure 1) of which shows the disappearance of the cinnamic acid double bond. The addition of hydrazine to the double bond was observed by Darapsky *et al.* (12) in the case of coumarin.

When hydrazine hydrate acted on the methyl ester of IX in more dilute solution and for a longer time, the product was found to have the structure XIV. Such a reducing action on double bonds by hydrazine hydrate has already been observed by Hanuš and Voříšek (18) in the oleic acid series.



ACKNOWLEDGMENT

We are indebted to E. H. Melvin and C. H. Van Etten of the Analytical and Physical Chemical Division of this Laboratory for the ultraviolet absorption spectra and the elementary analyses, respectively.

EXPERIMENTAL

All melting points are uncorrected.

α -Benzoylaminocinnamic acid hydrazide (VIII). Two grams of 2-phenyl-4-benzal-5-

oxazolone was triturated with 5 cc. of water, 15 cc. of methanol, and 4 cc. of 85% hydrazine hydrate until a clear solution resulted. A few minutes later white crystalline blades formed. After one hour at room temperature, 25 cc. of water was added and the reaction mixture kept at 0° overnight. Filtration gave 2.23 g. of fine white crystals which melted at 140–145° (evolution of gas) after air-drying. Recrystallization of this material from methanol-ethylene dichloride yielded 1.41 g. of air-dried product, m.p. 151–153° (gas evolution). Vanghelovici and Stephanescu report m.p. 153–154°. The compound analyzes as a monohydrate.

Anal. Calc'd for $C_{16}H_{17}N_3O_2 \cdot H_2O$: C, 64.20; H, 5.73; N, 14.04.

Found: C, 63.8; H, 6.00; N, 14.0 (Dumas).

Drying over phosphorus pentoxide to constant weight (three and one-half hours at 1 mm.) gave a very hygroscopic anhydrous product.

Anal. Calc'd for $C_{16}H_{17}N_3O_2$: C, 68.31; H, 5.38.

Found: C, 68.1; H, 5.50.

3-Phenyl-4-benzoylamino-5-pyrazolidone (X). Five grams of 2-phenyl-4-benzal-5-oxazolone was refluxed with 5 cc. of 85% hydrazine hydrate for thirty minutes. The crystals which deposited during the heating were triturated with water; yield, 3.83 g. Recrystallization from ethyl alcohol gave white needles of 3-phenyl-4-benzoylamine-5-pyrazolidone, m.p. 225–227° (Vanghelovici and Stephanescu, 229°).

Anal. Calc'd for $C_{18}H_{17}N_3O_2$: C, 68.31; H, 5.38; N, 14.94.

Found: C, 68.4; H, 5.66; N, 14.9 (Dumas).

2-Nitroso-3-phenyl-4-benzoylamino-5-pyrazolidone (XI). Two grams of 3-phenyl-4-benzoylamino-5-pyrazolidone (X) was dissolved in 100 cc. of concentrated hydrochloric acid. After addition of 100 cc. of water the solution was cooled to +5° and an equimolar amount (490 mg.) of sodium nitrite in 5 cc. of water was added gradually to the stirred liquid below the surface. A creamy precipitate appeared during the addition and was removed by filtration after ten minutes standing. The precipitate was immediately treated with 10 cc. of cold water containing 600 mg. sodium bicarbonate. A small amount of undissolved material was filtered off and the filtrate acidified with concentrated hydrochloric acid. The amorphous white precipitate which formed was separated and dried over phosphorus pentoxide at 0° *in vacuo*. It then melted at 107–110° with evolution of gas. The compound gave a deep red color with ferric chloride in alcohol; it also produced a deep blue color with a solution of diphenylamine in concentrated sulfuric acid (Angeli and Castellana modification of the Liebermann reaction). The nitroso compound was quite unstable at room temperature, some preparations giving nitrous fumes after only a few hours. Stored at 0° it appeared to be stable for some months. Because of the instability of the product and the difficulty of removing the solvent completely, the compound was analyzed as the barium salt, which retained two molecules of water of crystallization, even after long drying *in vacuo* over phosphorus pentoxide at 0°.

Anal. Calc'd for $C_{21}H_{20}BaN_2O_6 \cdot 2H_2O$: C, 48.52; H, 3.82; N, 14.15; Ba, 17.34.

Found: C, 48.9; H, 3.94; N, 13.8; Ba, 16.9.

α -Benzoylamino- β -hydrazinodihydrocinnamic acid hydrazide (XII). Five hundred mg. of methyl α -benzoylaminocinnamate was dissolved in the minimum amount (3 cc.) of methanol at room temperature and 0.5 cc. of 85% hydrazine hydrate added. In thirty minutes the clear solution deposited crystals which were filtered off at the end of two hours. Dried in air, the product (445 mg.) melted at 129–131° with vigorous evolution of gas, solidified and melted at 210–215°. This behavior suggested the elimination of hydrazine at the melting point with the formation of 3-phenyl-4-benzoylamino-5-pyrazolidone (X). To confirm this a sample of the addition compound was heated at 135° and 1 mm. pressure until evolution of gas ceased. The melting point of the resulting solid (220–224°) was not depressed by admixture with 3-phenyl-4-benzoylamino-5-pyrazolidone (X). The X-ray patterns of the two products were also identical.

The hydrazino compound slowly decomposes at room temperature. The melting point was lowered to 112–114° in four days. For analysis it was converted to the stable acetone

derivative XIII. One hundred mg. was dissolved in 8 cc. of acetone at room temperature. The crystals (84 mg.) which appeared were filtered off after several days, m.p. 194–196° (evolution of gas). Recrystallization from methanol gave 40 mg. of the product having the same melting point.

Anal. Calc'd for $C_{22}H_{27}N_3O_2$: C, 67.2; H, 6.92; N, 17.80.

Found: C, 67.3; H, 6.96; N, 17.6 (Dumas).

α -Benzoylamino dihydrocinnamic acid hydrazide (XIV). One hundred mg. of methyl α -benzoylamino cinnamate was dissolved in about 10% more ethanol than that required for solution at room temperature and 0.20 cc. of 85% hydrazine hydrate added. Crystals appeared after six days and one day later were filtered off; yield, 39 mg.; m.p. 186–187°. Recrystallization from methanol-ethanol gave 20 mg. of α -benzoylamino dihydrocinnamic acid hydrazide as needles melting at 189–190°.

Anal. Calc'd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83.

Found: C, 68.1; H, 6.00; N, 14.5

This hydrazide was shown by mixed melting point test and X-ray diffraction patterns to be identical with the hydrazide obtained from methyl α -benzoylamino dihydrocinnamic acid. The product could also be prepared in small yield (15 mg.) by heating 100 mg. of α -benzoylamino- β -hydrazinodihydrocinnamic acid hydrazide (XII) and 1 cc. of 85% hydrazine hydrate for three hours on the steam-bath.

SUMMARY

Under mild conditions hydrazine hydrate gives the expected hydrazide with 2-phenyl-4-benzal-5-oxazolone; at elevated temperature the product is 3-phenyl-4-benzoylamino-5-pyrazolidone. These structures differ from those assigned to the same products by Vanghelovici and Stephanescu. It has been found that the double bond in methyl- α -benzoylamino cinnamate adds hydrazine under some conditions and under other conditions the double bond is reduced.

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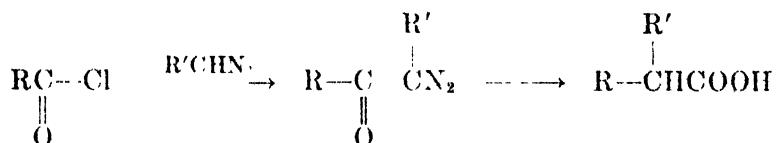
THE USE OF HIGHER DIAZOHYDROCARBONS IN THE ARNDT-EISTERT SYNTHESIS

A. L. WILDS AND ARTHUR L. MEADER, JR.¹

Received June 7, 1948

The Arndt-Eistert synthesis (1), involving reaction of an acid chloride with diazomethane followed by rearrangement of the resulting diazoketone, has become a well-established and useful method for converting an acid into a derivative of its next higher homolog. An excellent survey of the reaction and its uses has been made by Bachmann and Struve (2).

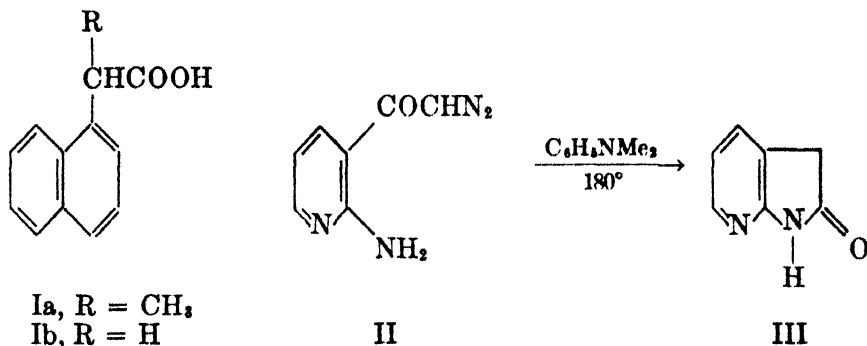
The synthesis apparently has not been employed with higher aliphatic diazohydrocarbons; the sole reference to such use which we have found in the literature is the statement by Eistert (3) that the diazoketone from *p*-nitrobenzoyl chloride and diazoethane may be rearranged to the anilide of α -(*p*-nitrophenyl)-propionic acid. Examples are known, however, in which diazoacetic ester has been employed, giving a substituted malonic ester after rearrangement (4). From these, the well-known rearrangement of phenylbenzoyldiazomethane ($\text{C}_6\text{H}_5\text{COCN}_2\text{C}_6\text{H}_5$) to diphenylketene (5), and the generally accepted mechanism for the Wolff rearrangement involving formation of a ketene intermediate (2, 6), it would be anticipated that higher diazohydrocarbons would give the α -substituted homolog in the Arndt-Eistert reaction.



We have investigated the use of diazoethane in this synthesis to determine if this course is taken by the reaction, and to explore the possibilities for using the reaction with the higher diazohydrocarbons as a synthetic tool. Treatment of 1-naphthoyl chloride with diazoethane under the usual conditions gave a yellow, oily diazoketone which evolved nitrogen when refluxed in methanol solution with silver oxide. Saponification of the resulting material gave a solid acid in 26% yield which was shown to be α -1-naphthylpropionic acid (Ia). In another run the acid was obtained in 34% yield, but in ten other attempts the reaction was unsuccessful, only neutral tars and a small amount of the starting acid being isolated. The technique was not at fault, for similar runs with diazomethane gave 1-naphthylacetic acid (Ib) consistently in 70% yield. The reason for these inconsistent results with diazoethane has not been discovered, but from the sequel it is probable that the major fault lay in failure of the diazoketone to undergo rearrangement.

¹ Wisconsin Alumni Research Foundation Research Assistant, 1946-1947; present address: California Research Corp., Richmond, California.

In the work with diazomethane, crystalline diazoketones usually were obtained, while with diazoethane the product was an oil. Even after a method was finally developed which gave crystalline diazoketones from diazoethane and *p*-chlorobenzoyl chloride or *p*-toluyl chloride, attempts to rearrange these pure diazoketones in methanol using silver oxide, silver nitrate, or copper powder met with failure. In all, six different diazoketones were tried. It was then noted that Kägi (7), after unsuccessful attempts to effect the Wolff rearrangement with the diazoketone II in the usual way, was able to rearrange it to the derivative III by heating at 180° with dimethylaniline. Arndt and Eistert (1) have also carried out several rearrangements to anilides by dropping the diazoketone into boiling aniline. In applying this last technique to the diazoketone from *p*-chlorobenzoyl chloride and diazoethane, nitrogen was evolved vigorously and an 85% yield of the anilide resulted. Similar results were obtained with the diazoketones from *p*-toluyl chloride and 1-naphthoyl chloride. Thus, a successful method for effecting the rearrangement was available.



In order for the synthesis to be generally useful, however, it was desirable to obtain a derivative more readily hydrolyzed than the anilides. Rearrangement at 170–180° in the presence of dimethylaniline and benzyl alcohol was found to give the benzyl esters which are easily hydrolyzed to the rearranged acids. This procedure has been applied many times to a number of different diazoketones derived from diazomethane, diazoethane, and diazopropane *without as yet a single failure*. Even with diazomethane it is not uncommon for occasional runs, for no apparent reason, to fail in the rearrangement step using the conventional method. This new method, then, appeared to be of considerable general value and was investigated in some detail.

Preparation of the diazohydrocarbons

For preparing diazoethane it has been our experience that the method of Adamson and Kenner (8), employing β -(N-nitrosoethylamino)isobutyl methyl ketone, is less satisfactory than the von Pechmann synthesis (9) using N-nitroso-N-ethylurethan. The latter method has been employed by Nirdlinger and Acree (10) for preparing several of the higher diazohydrocarbons, including diazoethane

and 1-diazopropane. We have developed a procedure for preparing diazoethane consistently in 75% yield by fairly rapid addition of the readily available nitrosoethylurethan to a solution of potassium hydroxide in *n*-propyl alcohol. When the addition was slow the yields were decreased to 30–50%. This improved method of preparing diazoethane makes it as readily available for use in organic reactions as diazomethane. In a similar manner 1-diazopropane was prepared in about 57% yield.

Preparation of the diazoketones

In the standard method for preparing diazoketones from diazomethane, the acid chloride is added to an excess (2.5 to 3.0 moles) of diazomethane at 0° and allowed to stand for several hours or even overnight at 0° to room temperature. In all of the runs which we have made with diazomethane this procedure gave practically quantitative yields of the crude crystalline diazoketone.

TABLE I

EFFECT OF TEMPERATURE ON THE PREPARATION OF 1-*p*-CHLOROBENZOYL-1-DIAZOETHANE

TEMP. °C.	YIELD OF CRYSTALLINE DIAZOKETONE, %	YIELD OF OILY DIAZOKETONE, %	TOTAL YIELD, %
5–10	48*	—	—
0–10	44	24	68
0	55	16	71
–10	61	12	73
–20	71	8	79
–30	61	10	71

* This material contained some of the by-product from further action of diazoethane.

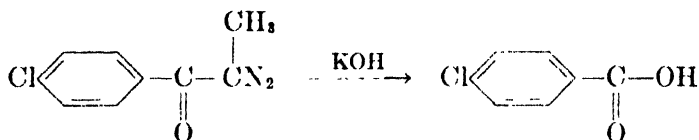
With diazoethane, however, it was found that the reaction conditions were more critical. In Table I are summarized runs with *p*-chlorobenzoyl chloride and diazoethane at various temperatures. The amount of oily diazoketone left in the filtrate was determined by rearrangement using benzyl alcohol and dimethylaniline and isolating the acid. It can be seen that the highest yield, both total and of crystalline material, was obtained at –20°. When the reaction was carried out above 0° a colorless by-product was obtained in addition to the yellow diazoketone. This by-product, $C_{11}H_{11}ClN_2O$, was shown to arise from the reaction of a second mole of diazoethane with the diazoketone with loss of nitrogen. A similar crystalline by-product, $C_{12}H_{14}N_2O$, was obtained from *p*-toluyl chloride. Although the structures of these compounds have not been elucidated, it is apparent that they are not diazoketones, for unlike the latter, they did not evolve nitrogen when treated with hydrobromic acid. We hope to establish the structure of these by-products in the near future.

This type of side reaction apparently is not of importance using diazomethane. Indeed 1-*p*-chlorobenzoyl-1-diazoethane was unaffected by diazomethane under conditions which gave the by-product with diazoethane. There are, however,

indications that such by-products may arise in certain cases. Lutz and co-workers (11) found that prolonged reaction of 5-chloro- and 5,8-dichloro-cinchonophen acid chlorides with a large excess of diazomethane resulted in mixtures containing considerably more than the expected amount of nitrogen, which suggests reaction with a second mole of diazomethane. Recently Fieser and Turner (12) isolated an anomalous by-product from the reaction of diazomethane with the acid chloride of 9-(2-acetoxy-1,4-naphthoquinonyl-3)-pelargonic acid. Although this compound was formulated as isomeric with the diazoketone, the analysis would also be consistent with a product resulting from addition of a second mole of diazomethane with loss of nitrogen.

Rearrangement of the diazoketones

As mentioned above, the usual silver oxide-methanol procedure was unsuited for rearrangement of a diazoketone from diazoethane, even when the crystalline compound was employed. In several cases, after an attempted rearrangement followed by alkaline hydrolysis, a considerable amount of the starting acid was isolated in addition to dark neutral tars. A separate experiment established the interesting fact that alkali can cleave a diazoketone derived from diazoethane:



Presumably the other fragment is diazoethane which undergoes further reaction, perhaps with the solvent or through decomposition.

For determining the optimum conditions of rearrangement using the benzyl alcohol method, 1-*p*-chlorobenzoyl-1-diazoethane was first heated with a series of high-boiling alcohols in the presence of dimethylaniline (see Table II). In each case the rearrangement took place, even when phenol was used. The best yields seemed to result with benzyl alcohol.

Next the effect of the tertiary amine was investigated, using benzyl alcohol (Table III). The yield was good in each case, ranging from 73 to 90%. The best results were obtained with γ -collidine (85–90%) and isoquinoline (86%). It is interesting to note that a tertiary amine is not essential, since even in its absence a 70% yield of the rearranged acid was obtained. However, the tertiary amine does improve the yields significantly. Triethanolamine and methyldiethanolamine are interesting examples which served both as the tertiary amine and the alcohol, giving 80 and 73% yields, respectively.

For establishing the effect of temperature a series of runs was made using benzyl alcohol and isoquinoline (Table IV). The reaction proceeded rapidly and in good yield at temperatures of 140–200°. At lower temperatures the reaction became slower and the yields dropped, although even at 80° the yield was 68%. The amount of starting acid recovered, though low in any case, was smallest at the highest temperatures. The optimum temperature appears to be around 170–190°.

Finally, to learn if the concentration had any effect, a series of runs was made in which the amount of benzyl alcohol was varied from 1 to 20 moles. The optimum seemed to be about 2-5 moles per mole of diazoketone (80-87% yields).

TABLE II

REARRANGEMENT OF 1-*p*-CHLOROBENZOYL-1-DIAZOETHANE IN THE PRESENCE OF VARIOUS ALCOHOLS

(Using 1 g. of diazoketone, 2.5 cc. of dimethylaniline, approximately 3 cc. of the alcohol, and heating for ten minutes, then hydrolyzing the ester).

ALCOHOL	BATH TEMP. °C	STARTING ACID RECOVERED, MG.	YIELD OF REARRANGED ACID, %
Benzyl..	170	—	74-81
Phenylethyl. . . .	170	40	53 ^a
Octanol-1.	170	45	78
Octanol-2.	165-170	55	73
2-Ethylhexanol-1	170	60	57
"Hexanol" ^b	150	46	53
Cyclohexanol .	160	9	70
Ethylene glycol .	170	0	71
Butyl carbitol.	170	24	64 ^c
Phenol..	170	31	71

^a Part of this product was lost.

^b A commercial mixture of hexanols.

^c This product was oily; the others were crystalline solids melting from 52-55° ("hexanol") to 55-57° (benzyl alcohol)

TABLE III

EFFECT OF THE TERTIARY AMINE

(Using 1 g. of 1-*p*-chlorobenzoyl-1-diazoethane, 5 cc. of benzyl alcohol and the tertiary amine at 165-170°)

TERTIARY AMINE (G.)	STARTING ACID RECOVERED, (MG.)	YIELD OF REARRANGED ACID, %
Dimethylaniline (3.8)	15	79
Diethylaniline (4.6)	24	80
γ-Collidine (3.8)	0-3	85-90
Quinoline (4.0)	16	75
Isoquinoline (4.0)	40	86
N- <i>n</i> -hexylpiperidine (5.2)	5	78
Triethanolamine ^a (4.6)	10	80
Methyl diethanolamine ^a (3.7)	30	73
None	55	70

^a No benzyl alcohol used in these runs.

In order to test the generality of the Arndt-Eistert synthesis with diazoethane as developed in this investigation, the reactions were applied to eight different acids, including one aliphatic and one arylaliphatic as well as aromatic acids (Table V). The over-all yields from the acid chloride ranged from 44 to 70%,

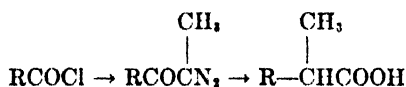
and with those examples which were worked out the most carefully they were in the range 55–70%. In three cases, acetic, 1-naphthoic and β -1-naphthylpropionic acids, the structure of the rearranged product was established by direct comparison with an authentic sample and in another case, *p*-nitrobenzoic acid,

TABLE IV
EFFECT OF TEMPERATURE

(Using 1 g. of 1-*p*-chlorobenzoyl-1-diazoethane, 5 cc. of benzyl alcohol and 5 cc. of isoquinoline; theoretical volume of nitrogen = 135 cc.)

BATH TEMP., °C	VOL. OF N ₂ , CC.	TIME NECESSARY FOR COMPLETION, MIN.	STARTING ACID RECOVERED, MG.	YIELD OF PRODUCT, %
200	140	0.5	6	86
190	135	1	7	87
180	122–135	1–2	13–16	83–84
170	135	2	11	86
160	125	2	6	81
150	130	2	21	81
140	130	4	18	82
120	125	8	24	77
100	122	30	31	76
80	134	420	36	68

TABLE V
ARNDT-EISTERT SYNTHESIS USING DIAZOETHANE



STARTING ACID	YIELD OF DIAZOKETONE	PRODUCT OF RE-ARRANGEMENT	YIELD IN REAR-RANGEMENT, %	OVER-ALL YIELD, %
Benzoic	(oil)	Anilide	—	55
<i>p</i> -Chlorobenzoic	71% + 7% oil	Acid	85–90	61–70
		Anilide	85	66
<i>p</i> -Toluic	51% + 16% oil	Acid	—	55–70
		Anilide	79	53
<i>p</i> -Nitrobenzoic	76%	Acid	66	50
		Anilide	60	46
1-Naphthoic	(oil)	Acid	—	58
		Anilide	—	36
2-Naphthoic	60%	Acid	67	40–48
β -1-Naphthylpropionic	(oil)	Acid	—	47
Acetic	(oil)	Anilide	—	44

the melting point of the product was in agreement with that described in the literature.

In a similar manner the synthesis was carried out using 1-diazopropane. With this reagent the acids were converted into their next higher homologs with an α -ethyl substituent, in yields ranging from 25 to 58% (see Table VI). The struc-

sure. In the case of *p*-nitrobenzoyl chloride the distilled product was recrystallized from benzene. The following table summarizes the results:

ACID CHLORIDE	B.P. (MM.)	YIELD %
<i>p</i> -Chlorobenzoyl	101-102 (12)	85
<i>p</i> -Toluyyl	94-95 (11)	87
<i>p</i> -Nitrobenzoyl	m.p. 71-71.5	44
<i>p</i> -Anisoyl	155.5-156 (30)	85
1-Naphthoyl	164-167 (13)	83
2-Naphthoyl	182-185 (25)	73

N-Ethyl-*p*-toluamide, prepared from the acid chloride and excess 33% aqueous ethylamine, crystallized from dioxane-water as colorless platelets, m.p. 96-97°; reported, 90° (13).

Anal. Calc'd for $C_{10}H_{13}NO$: C, 73.6; H, 8.0.

Found: C, 73.8, H, 8.0.

N-Ethyl-*p*-chlorobenzamide crystallized from dioxane-water as colorless needles, m.p. 110-111°.

Anal. Calc'd for $C_9H_{10}ClNO$: C, 58.8; H, 5.5.

Found: C, 58.4; H, 5.5.

β -(1-Naphthyl)propionic acid was prepared essentially by the procedure of Fieser and Gates (14) in 60% yield from 1-chloromethylnaphthalene (15). The acid chloride was prepared in benzene solution by warming gently for fifteen minutes with thionyl chloride and a trace of pyridine; several portions of benzene were added and removed under reduced pressure to eliminate the excess reagent.

Preparation of diazohydrocarbons

Diazomethane. For most of the runs the diazomethane was prepared from *N*-nitroso-*N*-methylurea as described in *Organic Reactions* (2). The ethereal solution was dried over potassium hydroxide pellets and distilled, giving diazomethane in 66% yield, as estimated by the benzoic acid method (see below).

Diazoethane. (a) From *N*-nitroso-*N*-ethylurethan. *N*-Ethylurethan was prepared by the method described in *Organic Syntheses* for *N*-methylurethan (17), except that 270 g. of 33% aqueous ethylamine was substituted for the methylamine. The yield of the colorless liquid was 86-92%, b.p. 59-60° (3 mm.) or 79-80° (14 mm.). The *N*-ethylurethan (234 g.; 2 moles) was nitrosated as described for the *N*-methyl derivative (18), resulting in 222-257 g. (76-88%) of pink liquid, b.p. 52.5-53.5° (5 mm.).

Diazoethane was prepared from the nitrosourethan in consistent yields of 75%, when the following procedure was followed closely. A 1-liter, three-necked flask was fitted with a dropping-funnel, mechanical stirrer, and a bent tube leading to a condenser set for downward distillation. The condenser was attached to an adapter which dipped below the surface of a little anhydrous ether in the receiver, a 500-cc. suction flask equipped with a drying-tube and cooled in an ice-bath. Although an all-glass joint apparatus is preferred, good results were obtained using tightly fitting corks coated with paraffin to protect them from the diazoethane. In a typical run 100 cc. of anhydrous ether and a solution of 25 g. of potassium hydroxide in 100 cc. of *n*-propyl alcohol were placed in the three-necked flask and warmed in a water-bath with stirring until the ether began to distill. Then, while the water-bath was held at 50°, a solution of 25 g. of *N*-nitroso-*N*-ethylurethan in 75 cc. of anhydrous ether was added rapidly from the dropping-funnel in five minutes or less, at such a rate that frothing was not serious. After addition of the reagent was complete, fresh portions of dry ether were added until the distillate was coming over colorless. The total volume of the deep orange solution was about 400 cc. and contained about 75% (128 millimoles)

of the theoretical amount of diazoethane, as estimated by the benzoic acid method (see below).

When the time of addition was lengthened to fifteen minutes the yield decreased to 66%, and when thirty minutes or longer, the yield was 30-50%.

(b) From *N*-nitroso- β -ethylaminoisobutyl methyl ketone. This reagent was prepared in 60-67% yields from mesityl oxide and 33% aqueous ethylamine essentially as described previously (8, 16), and observing the necessary precautions during distillation, 100-103° (1 mm.). Several different reagents were tried for the decomposition to diazoethane, including sodium in isopropyl alcohol, potassium hydroxide in *n*-propyl or isopropyl alcohol, and sodium in cyclohexanol. The best yields (around 46%) were obtained with the last reagent.

1-Diazopropane. *N*-*n*-Propylurethan was prepared by the method described for the *N*-methyl derivative using 100 g. of *n*-propylamine (Sharples Co.); the yield of colorless liquid, b.p. 92° (22 mm.) was 215 g. (97%). The urethan (215 g.) was nitrosated as described for the lower homolog, except that the product was not distilled;² the reddish oil amounted to 258 g. (98% yield) (10). 1-Diazopropane was prepared from the crude reagent using the procedure described above for diazoethane. When the reagent was added in five minutes the yield was 57%; when added in fifteen minutes the yield was 42%. The ether solutions of 1-diazopropane were slightly darker than those of diazoethane.

N-Nitroso-*N*-isopropylurethan. In a similar manner *N*-isopropylurethan was prepared from 100 g. of isopropylamine (Eastman Kodak Co.) and obtained in 90% yield as a colorless oil, b.p. 85° (19 mm.). Nitrosation of 199 g. gave 229 g. (94%) of crude, undistilled *N*-nitroso-*N*-isopropylurethan.³

N-Nitroso-*N*-butylurethan. *N*-*n*-Butylurethan, prepared in 83% yield, b.p. 71-72° (1 mm.), was nitrosated as before to give the nitrosourethan in 90% yield as a red oil which was not distilled.³ In a preliminary experiment a sample of the oil was converted to 1-diazobutane using ether and 40% potassium hydroxide as in the preparation of diazomethane from *N*-nitrosomethylurea (2). The deep orange ethereal solution of diazobutane was identified by reaction with 3,5-dinitrobenzoic acid, giving the *n*-butyl ester which without purification had the m.p. 60-63°; reported, 61-63° (19).

Estimation of the diazohydrocarbons.—The most satisfactory method used for determining the strength of the diazohydrocarbon solutions involved the addition of an aliquot at 0° to a weighed excess of benzoic acid dissolved in 50 cc. of dry ether. After standing for a few minutes 50 cc. of water and two drops of phenolphthalein solution were added and the solution titrated with 0.1 *N* sodium hydroxide with vigorous swirling (19a).

A second method which was used to check the purity of the diazohydrocarbon solution, involved adding an aliquot slowly to a cold solution of excess 3,5-dinitrobenzoic acid in dry ether. After reaction was complete the excess acid was removed by washing with potassium carbonate solution, then the ether solution was dried over potassium carbonate, filtered, and evaporated to dryness. The weight and melting point of the ester gave a measure of the amount of diazohydrocarbon and its purity. The results of duplicate determinations on the same solutions by the two methods are summarized in the following table:

DIAZOHYDROCARBON	BENZOIC ACID METHOD, %	3,5-DINITROBENZOIC ACID METHOD, %
Diazomethane	66	58, m.p. 106-107°
	64	59, (reported for pure ester, 110°)
Diazoethane	56	52, m.p. 92-93°
	59	58, (reported for pure ester 94°) (19)
1-Diazopropane	57	52, m.p. 70-72.5° (reported for pure ester, 75°) (19)

³ It is reported (10) that *N*-nitroso-*N*-*n*-butylurethan explodes when attempts are made to distill it.

Preparation of diazoketones

Diazoketones from diazomethane. These were prepared in the usual manner (2) by adding a solution of the acid chloride in dry ether dropwise to an ethereal solution of diazomethane (using 3 moles per mole of acid chloride). The solution was allowed to stand for two to twelve hours at 0–10° and then evaporated to dryness in the cold under reduced pressure. The crude solid diazoketones were used without purification. The following results were obtained:

p-Chlorobenzoyldiazomethane, crude yield 101%, m.p. 112–115°. A sample purified by recrystallization from petroleum ether (60–68°) as light yellow needles, m.p. 114–115°, gave low values for nitrogen (Found: N, 13.8; 13.8). When a sample was sublimed at 70° and 0.05 mm. followed by recrystallization from petroleum ether, m.p. 113–114.5°, satisfactory values were obtained.

Anal. Calc'd for $C_6H_5ClN_2O$: N, 15.5; Found (micro-Dumas): N, 15.1.

p-Toluyldiazomethane, crude yield 102%, m.p. 45–50°. Recrystallization from petroleum ether gave light yellow needles, m.p. 48–51°.

Anal. Calc'd for $C_7H_7N_2O$: N, 17.5; Found: N, 17.1.

p-Anisoyldiazomethane was obtained in 102% crude yield, m.p. 84–88°; reported for the pure compound, 90–91° (20).

1-Naphthoyldiazomethane was obtained in 100% crude yield, m.p. 48–50°; reported for the pure compound, 54–55° (1).

1-p-Chlorobenzoyl-1-diazoethane. The following procedure represented the optimum conditions in this case, and was typical for the preparation of diazoketones from diazoethane. To 355 cc. of an ethereal solution containing 131 millimoles of diazoethane, cooled to –20° in a Dry-Ice-alcohol bath (see Table I) was added dropwise with mechanical stirring a solution of 11.0 g. (62 millimoles) of *p*-chlorobenzoyl chloride in 50 cc. of anhydrous ether. The addition required fifteen minutes and the solution was stirred at –20° for an additional fifteen minutes, after which the excess diazoethane was removed under reduced pressure, still keeping the solution at –20°. When the excess diazoethane was gone (as indicated by the lightening in color of the solution) the remainder of the solvent was removed at 0°. The residual diazoketone, which crystallized, was triturated with ice-cold petroleum ether, giving 7.87 g., m.p. 50–52.5°. Additional crops obtained by cooling, finally to –80°, amounted to 0.55 g., m.p. 50–52°, and 0.26 g., m.p. 49–51°, bringing the total to 71%. By recrystallization from petroleum ether yellow prisms, m.p. 56–57.5°, were obtained.

Anal. Calc'd for $C_7H_7ClN_2O$: N, 14.4; Found, N, 14.4.

The oily residue from the filtrate, dissolved in 7 cc. of benzyl alcohol and 8 cc. of dimethylaniline, was heated in an oil-bath at 170° for five minutes and worked up as described below. In addition to 0.28 g. (3%) of *p*-chlorobenzoic acid, m.p. 236–237°, 0.88 g. (8%) of α -(*p*-chlorophenyl)propionic acid was obtained, m.p. 52.5–55.5°, indicating the total amount of diazoketone to be at least 79%.

*α -Bromo-*p*-chloropropiophenone.* To a solution of 0.5 g. of the above diazoketone in ether was added 48% hydrobromic acid dropwise until the evolution of nitrogen ceased. From the ether layer by evaporation and crystallization of the residue from dilute alcohol was obtained 0.52 g. (82%) of the bromoketone as colorless plates, m.p. 77–79°; reported, 77.5° (21).

Alkaline cleavage of 1-p-chlorobenzoyl-1-diazoethane. To 1 g. of the diazoketone was added 5 cc. of 45% potassium hydroxide and 5 cc. of methanol. There was a distinct warming of the solution with evolution of nitrogen and formation of a black insoluble tar. When the solution was warmed further another gas with an ethereal odor was evolved (methyl ethyl ether?). After refluxing for four hours the diluted solution was extracted with ether to remove the non-acidic fraction. The alkaline solution was acidified, extracted with ether, evaporated and the residue was digested with hot petroleum ether (60–68°), giving 0.28 g. (35%) of *p*-chlorobenzoic acid, m.p. 235–237°. From the filtrate was obtained an additional 0.05 g., m.p. 180–200°.

1-p-Toluyyl-1-diazoethane was prepared from 2.09 g. of *p*-toluyyl chloride as described for the *p*-chloro derivative, allowing the reaction mixture to stand at -20° for one hour after addition was complete. The product, a yellow oil, was crystallized from petroleum ether by cooling with Dry-Ice-ether, giving 1.15 g. (49%) of the crystalline derivative, m.p. $51-52^{\circ}$. Recrystallization from petroleum ether gave yellow prisms, m.p. $52-53^{\circ}$.

Anal. Calc'd for $C_{10}H_{10}N_2O$: N, 16.1; Found; N, 15.9.

*α -Bromo-*p*-methylpropiophenone* was prepared from the above diazoketone by treating a dioxane solution with 48% hydrobromic acid and crystallizing the product from dilute alcohol; yield 65%, m.p. $70-75^{\circ}$. Recrystallization from petroleum ether raised the m.p. of the solid to $78-78.5^{\circ}$; reported, $76-77^{\circ}$ (22).

1-(p-Nitrobenzoyl)-1-diazoethane was prepared from 10 g. of *p*-nitrobenzoyl chloride as described above for *p*-chloro derivative. The diazoketone crystallized from the reaction mixture, 7.49 g., m.p. $109-110^{\circ}$ dec., and from the filtrate by concentration under reduced pressure was obtained an additional 0.76 g., m.p. $106.5-108^{\circ}$ dec., and 0.22 g., m.p. $105-107^{\circ}$ dec., for a total of 76%. Recrystallization from ether gave yellow needles, m.p. $109.5-110^{\circ}$ dec.

Anal. Calc'd for $C_9H_7N_2O_3$: N, 20.5; Found: N, 20.8.

1-(2'-Naphthoyl)-1-diazoethane, prepared as above from 2.43 g. of 2-naphthoyl chloride, gave 1.37 g. of bright yellow needles, m.p. $109-110^{\circ}$ dec., from the original reaction mixture and an additional 0.54 g., m.p. $98-104^{\circ}$ dec., and 0.17 g., m.p. $85-95^{\circ}$ dec., from the filtrate for a total yield of 78%. The melting point of the material in the first crop was not raised by further recrystallization from petroleum ether.

Anal. Calc'd for $C_{12}H_{10}N_2O$: C, 74.3; H, 4.8.

Found: C, 74.1; H, 4.8.

Other diazoketones from diazoethane. In a similar manner were prepared the diazoketones from diazoethane and acetyl chloride, benzoyl chloride, 1-naphthoyl chloride and β -(1-naphthalene)propionyl chloride. These diazoketones were obtained as yellow oils and were used in the rearrangement step without purification.

By-product from p-toluyyl chloride and diazoethane. (a) *Prepared from toluyyl chloride.* When a solution of 1.5 g. of *p*-toluyyl chloride was added to excess diazoethane solution at 0° and allowed to stand at room temperature for sixteen hours before removing the ether, crystallization of the product from petroleum ether gave 0.45 g. (25%) of colorless needles, m.p. $78-80^{\circ}$.

(b) *From the diazoketone and diazoethane.* When 0.7 g. of 1-*p*-toluyyl-1-diazoethane and a solution of 18 millimoles of diazoethane in 50 cc. of ether were allowed to stand at room temperature for two and one-half hours, crystallization of the residue gave 0.11 g. (14%) of the by-product as colorless needles, m.p. $78-80^{\circ}$. On further crystallization the m.p. of the sample was raised to $80.5-81^{\circ}$. The compound decomposed to an oil with evolution of gas upon standing at room temperature for fifteen to twenty hours. Unlike the diazoketone it did not evolve nitrogen when treated with hydrobromic or acetic acid.

Anal. Calc'd for $C_{12}H_{14}N_2O$: C, 71.3; H, 7.0; N, 13.9.

Found: C, 70.9, 71.0, 71.1; H, 6.8, 6.9, 6.9; N, 13.4.

By-product from p-chlorobenzoyl chloride and diazoethane. (a) *Prepared from the acid chloride.* From 1.5 g. of *p*-chlorobenzoyl chloride and diazoethane as described above for the *p*-toluyyl derivative was obtained 0.52 g. (27%) of pale yellow needles, m.p. $86-86.5^{\circ}$.

(b) *From the diazoketone and diazoethane.* When 1 g. of 1-*p*-chlorobenzoyl-1-diazoethane and a solution of 18 millimoles of diazoethane in 50 cc. of ether were allowed to stand at room temperature for four hours, a total of 0.47 g. (41%) of the by-product could be crystallized from petroleum ether, m.p. $88.5-90^{\circ}$. Recrystallization of a sample from petroleum ether gave colorless needles, m.p. $90.5-91^{\circ}$, which decomposed to an oil upon standing at room temperature, but evolved no gas when treated with acid.

Anal. Calc'd for $C_{11}H_9ClN_2O$: C, 59.3; H, 5.0; N, 12.6.

Found: C, 59.0, 59.3, 59.6; H, 5.0, 4.9, 5.1; N, 12.4.

(c) *Action of diazomethane on 1-p-chlorobenzoyl-1-diazoethane.* When 1 g. of the diazo-

ketone (m.p. 52–54°) was treated with ethereal diazomethane and allowed to stand at room temperature for twenty hours, 88% of the diazoketone was recovered, m.p. 51–54°, with an additional 10% of yellow oil which evolved nitrogen vigorously when treated with acid. This indicated no appreciable reaction between this diazoketone and diazomethane under these conditions.

1-p-Nitrobenzoyl-1-diazopropane.—To a solution of 20 millimoles of diazopropane in 230 cc. of ether at –20° was added with stirring 1.85 g. (10 millimoles) of *p*-nitrobenzoyl chloride in 30 cc. of dry ether over a fifteen-minute period. After an additional thirty minutes at –20° the solution was concentrated under reduced pressure to about 150 cc. and filtered, giving 1.39 g. of yellow needles, m.p. 97–98° dec. From the filtrate was obtained 0.39 g., m.p. 96.5–98° dec., and 0.07 g., m.p. 83–87° dec. The first two crops corresponded to a yield of 81%. The analytical sample crystallized from petroleum ether as yellow prisms, m.p. 97.5–98.5° dec. The compound dissolved in acetic acid with slow evolution of nitrogen.

Anal. Calc'd for $C_{10}H_9N_3O_3$: N, 19.2; Found: N, 18.9.

Other diazoketones from 1-diazopropane. In a similar manner were prepared the diazoketones from 1-diazopropane and acetyl chloride, *p*-chlorobenzoyl chloride, and *p*-anisoyl chloride. These derivatives, obtained as yellow oils, were used for rearrangement without purification.

Rearrangement of the diazoketones—general methods

The benzyl alcohol-tertiary amine method.—The benzyl alcohol used here was purified by shaking for one hour with saturated sodium bisulfite solution and allowing to stand overnight. The benzyl alcohol layer was then shaken with 45% potassium hydroxide, dried over potassium carbonate and distilled under reduced pressure, collecting the fraction b.p. 92–94° (12 mm.).

For the rearrangement reaction, the diazoketone (1.0 g.) was dissolved in a mixture of purified benzyl alcohol (about 5 cc.) and a high-boiling tertiary amine (about 5 cc.). The solution was heated rapidly to the desired temperature by immersing the flask (attached to reflux condenser) in a preheated oil-bath, usually at 170–190°. After an induction period of a few seconds a vigorous evolution of nitrogen occurred. The reaction was usually over in a few minutes at 170° or higher. After heating about five minutes, the solution was cooled, ether added, and the extract washed twice with dilute hydrochloric acid. Following removal of the ether the oily ester was hydrolyzed by heating with methanol (5 cc.) and 45% potassium hydroxide (5 cc.) for two to four hours. (In the case of the nitro compounds the hydrolysis was effected by heating with 10 cc. of hydrochloric and 10 cc. of acetic acids for eighteen to twenty-four hours.) The methanol was then evaporated and the alkaline solution extracted twice with ether before acidifying. Ether extraction gave the crude acid which was purified by recrystallization or evaporative distillation.

With large runs it was advantageous to add the solid diazoketone in portions to the hot alcohol-amine mixture, since in this way the rate of evolution of gas could be controlled.

Aniline method. A solution of the diazoketone (1.0 g.) in freshly distilled aniline (5 cc.) was immersed in an oil-bath preheated to 180°. After the vigorous reaction was over, the mixture was poured onto ice and concentrated hydrochloric acid, and the anilide was purified by recrystallization.

Silver oxide-methanol method. This procedure was essentially as described in *Organic Reactions* (2).

Rearrangement of diazoketones related to diazomethane

The results are summarized in Table VIII. For the four runs in which the silver oxide-methanol and benzyl alcohol- γ -collidine methods are compared, the same sample of diazoketone was used for each method.

Rearrangement of diazoketones related to diazoethane

Using 1-*p*-chlorophenyl-1-diazoethane. For the alcohol-tertiary amine method the results using different alcohols are given in Table II, with different amines in Table III and varying the temperature in Table IV. For each of these runs the standard procedure with 1 g. of diazoketone was followed except for the variation noted in the Tables. The crude acidic product was digested with 10-12 cc. of hot petroleum ether (60-68°), allowed to stand at room temperature and filtered to remove *p*-chlorobenzoic acid. The acid in the filtrate was

TABLE VIII
REARRANGEMENT OF DIAZOKETONES RELATED TO DIAZOMETHANE

DIAZOKETONE RCOCHN_2 $\text{RCO} =$	WEIGHT G.	METHOD OF REARRANGEMENT	PRODUCT ISOLATED (RCH_2COOH ETC.)	% YIELD	M.P. °C.	M.P. REPORTED (REF.) °C
Benzoyl	^a	Silver oxide-ethanol	Acid	40	76-77	76-77
<i>p</i> -Nitrobenzoyl	^b	Silver oxide-methanol	Methyl ester	62	50.5-51	54 (24)
<i>p</i> -Chlorobenzoyl	1	Silver oxide-methanol	Acid	64	100-103 ^c	105-106 (25)
"	1	Benzyl alcohol- γ -collidine	Acid	68	104-105	105-106 (25)
<i>p</i> -Toluyyl	1	Silver oxide-methanol	Unsuccessful	0	—	94 (26)
"	1	Benzyl alcohol- γ -collidine	Acid	79	87-91.5	94 (26)
<i>p</i> -Anisyl	1	Silver oxide-methanol	Unsuccessful	0	—	85-87 (20)
"	1	Benzyl alcohol- γ -collidine	Acid	69-76 ^d	80-84	85-87 (20)
1-Naphthoyl	1	Silver oxide methanol	Acid	67	131-133	131.5 (27)
"	1	Benzyl alcohol- γ -collidine	Acid	74	130-133	131.5 (27)

^a From 10 g. of benzoyl chloride; crude diazoketone, m.p. 44-46°.

^b From 5 g. of *p*-nitrobenzoyl chloride.

^c About one-third of product m.p. 93-102°.

^d The higher yield was obtained when the solid diazoketone was added to the hot alcohol-amine mixture.

evaporatively distilled at 100-120° (0.1 mm.) giving crystalline α -*p*-chlorophenylpropionic acid in the yield reported. The analytical sample crystallized from petroleum ether as colorless crystals, m.p. 57-58°.

A larger run, carried out by adding 9 g. of the solid diazoketone to a hot (150-180°) mixture of 28 g. of γ -collidine and 25 g. of benzyl alcohol gave an 83% yield of the rearranged acid, m.p. 47-55°.

Another run in which the diazoketone from 3.25 g. of *p*-chlorobenzoyl chloride was not isolated but the entire product rearranged gave 0.21 g. (7%) of *p*-chlorobenzoic acid, m.p. 236-238°, and 2.08 g. (61%) of α -*p*-chlorophenylpropionic acid, m.p. 50-55°.

Using 1-*p*-nitrobenzyl-1-diazoethane. In one run, starting with 2.4 g. of the diazoketone

TABLE IX
REARRANGEMENT OF DIAZOKETONES RELATED TO DIAZOTETRAHE
(Using benzyl alcohol-tertiary amine method except where noted)

DIAZOKETONE $\begin{array}{c} \text{CH}_3 \\ \\ \text{R}-\text{CO}-\text{CN} \\ \\ \text{R}'\text{CO}-\text{O} \end{array}$	WEIGHT G.	TERTIARY AMINE	TEMP. °C	PRODUCT ISOLATED $\begin{array}{c} \text{CH}_3 \\ \\ \text{R}-\text{CH}-\text{COOH} \end{array}$	YIELD %	M.P. °C	M.P. °C REPORTED (REF)	ANAL. FOUND	
								C	H
Benzoyl	^b	Aniline ^c	190	Anilide	55 ^d	131 -132	—	80.0 ^e	7.0 ^e
<i>p</i> -Chlorobenzoyl	1	γ -Collidine (see Table III)	170	Acid	85-90	57 -58	—	58.6 ^f	4.8 ^f
"	0.5	Aniline ^c	165	Anilide	78	154.5-155	—	69.4 ^g	5.6 ^g
<i>p</i> -Toluyll	^a	γ -Collidine	190	Acid	70 ^d	not completely pure	34 -35 (28)	—	—
"	0.7	Aniline ^c	170	Anilide	79	132.5-133	—	80.3 ⁱ	7.1 ⁱ
<i>p</i> -Nitrobenzoyl	1	γ -Collidine	160	Acid	66	88 -89	87 -88 (29)	—	—
"	1	Aniline ^c	165	Anilide	60	159 -159.2	—	66.4 ^j	5.4 ^j
1-Naphthoyl	^a	γ -Collidine	180	Acid	58 ^d	146 -148 ⁱ	148 -149 (30)	—	—
"	^m	Aniline ^c	150	Anilide	38 ^d	150 -154 ⁱ	154.5-155.5 ^g	—	—
2-Naphthoyl	ⁿ	γ -Collidine	190	Acid	48 ^d	129.5-130	—	78.1 ^r	5.8 ^r
β -1-Naphthylpropionyl	^o	γ -Collidine	190	Acid	47 ^d	83 -83.5 ⁱ	83 -84 (31)	—	—
Acetyl	^p	Aniline ^c	165	Anilide	44 ^d	104 -105 ⁱ	104.5-105.5 ^g	—	—

^a The yield is for material melting within a few degrees of the purest samples unless otherwise noted.

^b Using the oily diazoketone from 2.06 g. of benzoyl chloride.

^c No benzyl alcohol used here.

^d Over-all yield from acid chloride (or acid in some cases).

^e Calc'd for $\text{C}_{12}\text{H}_{11}\text{NO}$: C, 80.9; H, 6.7.

^f Calc'd for $\text{C}_8\text{H}_7\text{ClO}_2$: C, 58.5; H, 4.9.

^g Calc'd for $\text{C}_{12}\text{H}_{11}\text{ClNO}$: C, 69.4; H, 5.4.

^h Using the entire diazoketone from 2.23 g. of *p*-toluyl chloride.

ⁱ Calc'd for $\text{C}_{12}\text{H}_{11}\text{NO}$: C, 80.3; H, 7.1.

^j Calc'd for $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_2$: C, 66.7; H, 5.2.

^k Using the oil diazoketone from 4.25 g. of 1-naphthoyl chloride.

^l Mixed m.p. with an authentic sample undepressed.

^m Using oily diazoketone from 2.5 g. of 1-naphthoyl chloride.

ⁿ Using the entire diazoketone from 2.52 g. of 2-naphthoic acid through the acid chloride.

^o Using the oily diazoketone from 2.82 g. of β -1-naphthylpropionic acid through the acid chloride.

^p Using the oily diazoketone from 1.38 g. of acetyl chloride.

^q Pure sample prepared from the acid.

^r Calc'd for $\text{C}_{12}\text{H}_9\text{O}_2$: C, 78.0; H, 6.0.

and heating with 1.2 g. of benzyl alcohol and 6 g. of γ -collidine at 180° for three minutes, the intermediate benzyl ester was isolated by washing the ether extract of the reaction mixture with dilute acid and water, and then distilling. The fraction, b.p. 173–179° (0.1 mm.) was redistilled at 140–150° (0.05 mm.) to give 1.87 g. (59%) of benzyl α -(*p*-nitrophenyl)propionate.

Anal. Calc'd for $C_{16}H_{15}NO_4$: C, 67.4; H, 5.3.

Found: C, 67.4; H, 5.3.

Hydrolysis of a sample of the ester by heating with hydrochloric and acetic acids for eighteen hours, gave the acid, m.p. 86–87.5°.

With other diazoketones. The results are summarized in Table IX.

The following derivatives were prepared for comparison starting with acid chloride from authentic α -(1-naphthyl)propionic acid (30):⁴

Amide, colorless needles from dioxane-water, m.p. 127–128°.

Anal. Calc'd for $C_{15}H_{13}NO$: C, 78.4; H, 6.6.

Found: C, 78.2; H, 6.5.

TABLE X
REARRANGEMENT OF DIAZOKETONES RELATED TO 1-DIAZOPROPANE

DIAZOKETONE C_6H_5 $RCOCHN_2$ $RCO-$	WEIGHT	TERTIARY AMINE	TEMP. °C	PRODUCT ISOLATED C_6H_5 $RCHCOOH$	YIELD %	M.P. °C	M.P. °C REPORTED (REF.)
Acetyl	•	Aniline ^b	170	Anilide	25°	109.5–110.5	110–111 (32)
<i>p</i> -Chloro- benzoyl	•	γ -Collidine	200	Acid	58°	crude 76–81 pure 81.5–82.5	
<i>p</i> -Nitro- benzoyl	1 g	γ -Collidine	165	Acid	56	crude 112–118 pure 120–121.5°	121–122.5 (33)
<i>p</i> -Anisoyl	•	γ -Collidine	165	Acid	37°	crude 52–58 pure 62–63.5°	66–67 (33)

• Using the oily diazoketone from 2.6 g. of acetyl chloride.

^b No benzyl alcohol used here.

• Over-all yield from acid chloride.

⁴ Using oily diazoketone from 1.86 g. of *p*-chlorobenzoyl chloride.

• *Anal.* Calc'd for $C_{10}H_{11}ClO_2$: C, 60.4; H, 5.6. Found: C, 60.6; H, 5.8.

¹ Using oily diazoketone from 5.53 g. of anisoyl chloride.

• Mixed m.p. with an authentic sample undepressed.

Anilide, colorless needles from 80% alcohol, m.p. 154.5–155.5°.

Anal. Calc'd for $C_{15}H_{17}NO$: C, 82.9; H, 6.2.

Found: C, 82.7; H, 6.1.

Attempts to use the silver oxide-methanol method. In eleven attempts to use this method with the oily diazoketone from 1-naphthoyl chloride and diazoethane, the reaction was successful in two trials, giving 26% and 34%, respectively, but in nine other attempts it was unsuccessful, probably because the diazoketone did not undergo rearrangement. In these cases large amounts of neutral tar and in several runs some 1-naphthoic acid were obtained. In one run a small amount (10%) of the amide of the rearranged product was prepared using silver nitrate and ammonium hydroxide in dioxane solution.

The silver oxide-methanol rearrangement was also unsuccessful using the crystalline

⁴ This acid was synthesized by Richard S. Schiefelbein (B.S. Thesis, University of Wisconsin, 1943) by a method similar to that published subsequently by Blicke and Feldcamp (30).

1-*p*-chlorobenzoyl-1-diazoethane (32% of *p*-chlorobenzoic acid obtained after alkaline hydrolysis), with 1-*p*-toluyl-1-diazoethane (42% of *p*-toluic acid obtained), 1-*p*-nitrophenyl-1-diazoethane, 1-(2'-naphthoyl)-1-diazoethane and the oily 1-(β -1'-naphthyl-1-propionyl)-1-diazoethane.

Rearrangement of diazoketones related to 1-diazopropane

These reactions, carried out with benzyl alcohol and γ -collidine by the standard procedure, are summarized in Table X. There is some indication that the *n*-propylamine used to prepare the 1-diazopropane was not entirely pure, which may account in part for the lower yields and less pure products in this series.

SUMMARY

1. Procedures have been developed which make it possible to use the Arndt-Eistert reaction with higher diazohydrocarbons.
2. The reaction has been employed with diazoethane and 1-diazopropane to prepare α -methyl and α -ethyl homologs, respectively, of the starting acid.
3. An improved method for effecting rearrangement of the diazoketones was developed, involving heating at 180–190° with benzyl alcohol and a tertiary amine.

MADISON 6, WIS.

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THE PAPILIONACEOUS ALKALOIDS. VI. *LUPINUS PUSILLUS*, PURSH.¹

LÉO MARION AND STUART W. FENTON

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In continuation of the investigation in this series, the isolation of the alkaloids of *Lupinus pusillus*, Pursh., is now reported. The plant was collected in southern Alberta and placed at our disposal through the generosity of Dr. R. H. F. Manske. It contains at least four alkaloids, three of which, *i.e.*, *d*-sparteine (1), anagyrine (rhombinine) (2, 3), and *l*-lupanine (4), have been isolated previously from other sources.

The fourth alkaloid appears to be new and it is proposed to designate it pusilline. Its empirical formula, $C_{15}H_{23}N_2$, differs from that of sparteine in containing two more H atoms. Its properties are closely related to those of sparteine from which it is difficult to separate and, in common with that alkaloid, it forms a monoperchlorate which crystallizes from an aqueous solution only after the addition of a little ammonia. Pusilline contains one methylimino group and it forms a methiodide which does not undergo the Hofmann degradation, but is converted back to the original base.

EXPERIMENTAL

The dried and ground plant material (1200 g.) was extracted with methanol in Soxhlet extractors. The combined extract was distilled until the solvent had been largely removed and the residue was diluted with water, acidified with hydrochloric acid, and kept on the steam-bath overnight. The crude alkaloid obtained according to the process already described (4), consisted of a viscous oil weighing 13.6 g. It was distilled *in vacuo* and the following fractions were obtained: I, b.p. 100–110° (0.2 mm.), a colorless oil, wt. 5.05 g.; II, b.p. 120–135° (0.2 mm.), a thick, colorless oil, wt. 0.72 g.; III, b.p. 140–155° (0.2 mm.), a thick colorless oil, wt. 2.15 g.; IV, b.p. 160–175° (0.2 mm.), a thick oil, wt. 1.46 g., and a residue.

Isolation of pusilline. The oil obtained as fraction I [b.p. 100–110° (0.2 mm.)] was dissolved in a small volume of methanol and the solution made just acid to Congo Red with 65% perchloric acid. A crystalline perchlorate, which separated during the addition of the acid, had all dissolved again when the addition was completed. Water was added to the solution, which was heated on the steam-bath until the methanol had evaporated. Even on long standing, no perchlorate separated from the aqueous solution, but the addition of a few drops of ammonium hydroxide caused immediate crystallization. The filtered perchlorate, after several recrystallizations from boiling methanol, consisted of fine, colorless needles, m.p. 219.5°.²

Anal. Calc'd for $C_{15}H_{23}N_2 \cdot HClO_4$: C, 53.49; H, 8.62; N, 8.32; Imino-CH₃, 4.46.

Found: C, 54.08, 54.13; H, 8.74, 8.62; N, 8.22, 8.37; Imino-CH₃, 4.41.

The free base, recovered from the perchlorate, could not be induced to crystallize; it is levorotatory, $[\alpha]_D^{25} -15.3^\circ$ ($c = 2.3$ in abs. ethanol). No definitely crystalline picrate could be obtained.

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² All melting points are corrected.

Isolation of d-sparteine. After concentration, the methanolic mother liquor from which pusilline perchlorate had separated, yielded a second perchlorate, m.p. 170–173°. A mixture of this salt with an authentic sample of *d*-sparteine monoperchlorate (m.p. 173°) melted at 172–173°. The base recovered from the perchlorate and distilled [b.p. 98–100° (0.2 mm.)], had $[\alpha]_D^{25} + 16.6^\circ$ ($c = 0.87$ in abs. ethanol); when dissolved in methanol and added to a boiling methanolic solution of picric acid, it yielded a picrate. After several recrystallizations from boiling methanol, this picrate was obtained as pale yellow needles, m.p. 208.5°. The melting point was not altered by admixture of the picrate with *d*-sparteine dipicrate, but was depressed by admixture with *l*-sparteine dipicrate.

Isolation of l-lupanine. Fraction III could not be induced to crystallize. It was, therefore, dissolved in methanol and the solution made just acid to Congo Red by the cautious addition of 65% perchloric acid. A crystalline perchlorate separated immediately which, after several recrystallizations from boiling methanol, consisted of stout, colorless prisms, m.p. 213°, either alone or after admixture with *l*-lupanine perchlorate (2, 4). The identity is also confirmed by the optical rotation of the salt, $[\alpha]_D - 40.1^\circ$ ($c = 1.3$ in water), which agrees with that of *l*-lupanine perchlorate (2, 4). The oil obtained as fraction II, when neutralized with perchloric acid, yielded further quantities of pusilline perchlorate and *l*-lupanine perchlorate.

Isolation of anagyrine. Fraction IV, b.p. 160–175° (0.2 mm.), was converted to the perchlorate in the usual manner. After two recrystallizations from boiling methanol, from which it separated as fine, colorless needles, the perchlorate melted at 315° (dec.), either alone or after admixture with anagyrine perchlorate (m.p. 315°) (2, 3). A quantity of the perchlorate was decomposed with aqueous ammonia and the liberated base extracted with chloroform. After evaporation of the chloroform, the residual base was distilled, b.p. 165–170° (0.1 mm.), and converted in methanolic solution to the picrate which, after two crystallizations from boiling methanol, melted sharply at 253°, either alone or after admixture with anagyrine picrate (m.p. 253°).

Pusilline methiodide. To a solution of pusilline (0.244 g.) in ethyl acetate (5 cc.), methyl iodide (0.185 g.) was added and the solution allowed to stand at room temperature in a stoppered flask. A white, crystalline methiodide separated rapidly which, after three recrystallizations from ethyl acetate, melted at 260°.

Anal. Calc'd for $C_{16}H_{23}N_2 \cdot CH_3I$: C, 50.79; H, 8.26.

Found: C, 50.76; H, 8.07.

Pusilline methiodide does not undergo the Hofmann degradation, and on treatment with moist silver oxide gives a quantitative yield of pusilline.

SUMMARY

Lupinus pusillus, Pursh., contains at least four alkaloids, i.e., *d*-sparteine, *l*-lupanine, anagyrine, and a new alkaloid, pusilline. Pusilline, $C_{16}H_{23}N_2$, differs from sparteine in containing two more H atoms, and it is similar to it in properties.

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THE REACTION OF SUCROSE WITH ETHYLENE OXIDE¹

J. W. LEMAISTRE² AND RAYMOND B. SEYMOUR

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Although the addition of ethylene oxide to starch (3) and cellulose (2) has been reported, no instance of a reaction of this type with sugars of low molecular weight has been found in the literature. We have, therefore, studied the action of ethylene oxide on sucrose.

Sucrose and ethylene oxide did not react appreciably in neutral aqueous solution or in liquid ethylene oxide but reacted readily at room temperature in aqueous sodium hydroxide solution. Reactions were carried out with molar ratios of ethylene oxide to sucrose of 1, 2, 3, 4, and 11. In all cases the ethylene oxide was entirely converted to non-volatile products and only in the first case could any unchanged sucrose be recovered from the reaction mixtures. The products were gummy or glassy mixtures whose sweetness decreased with increasing ethylene oxide content. Attempts to separate these mixtures into their components were not very successful. One crystalline substance was isolated in small yield by utilizing as seeds a few crystals which appeared spontaneously in some of the mixtures. The composition of this material agreed essentially with that calculated for a bis-(β -hydroxyethyl)sucrose. Figure 1 shows a photomicrograph of the crystals.

The products of these reactions were gums which were soluble in water, methanol, and pyridine and insoluble in ether, chloroform, and acetone. Their solubility in ethanol and dioxane increased with the proportion of ethylene oxide. They were hygroscopic in about the same degree as glycerol. They did not depress the surface tension of water except when the molar ratio of ethylene oxide to sucrose was 4:1 or over and then the effect was small. In this respect the addition products resembled sucrose (1).

Since it did not appear feasible to isolate the individual components of the reaction mixtures, indirect evidence was obtained that these were addition products and not mixtures of sucrose with polyethylene glycols. The reacted mixtures had about the same observed optical rotations as the original sucrose solutions, but acid hydrolysis of the former gave final values of rotation that differed significantly from those obtained by inverting the sucrose solutions. These inverted solutions also differed from those of sucrose in their reaction with phenylhydrazine. As the ratio of ethylene oxide to sucrose increased, the yield of D-glucose phenylosazone decreased. When the molar ratio exceeded two to one, orange-red oils only were obtained rather than crystalline osazone. Further, the acetylation of the reaction products gave acetates whose saponification

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² Present address Chattam Chemical Co., Chattanooga, Tennessee.

equivalents agreed with the values calculated for sucrose-ethylene oxide addition products.

The results of the work indicate that the major reaction of ethylene oxide with sucrose proceeds in the expected manner by addition of the epoxide at hydroxyl groups of the sugar.



Figure 1 Addition Product of Sucrose and Ethylene Oxide ($\times 60$)

PROCEDURE

Reaction of sucrose with ethylene oxide A solution of 34.3 g. of sucrose in 150 g. of 0.25 *N* aqueous sodium hydroxide was treated with ethylene oxide gas until the desired weight had dissolved. Alternatively, liquid ethylene oxide could be added to the cold sucrose solution. The flask was stoppered and left at room temperature for twenty-four hours. The solution was then run slowly through a 2 \times 50 cm. column of Amberlite IR-100 H³ to remove sodium hydroxide. Yields of crude reaction product determined at this point by evaporating aliquot samples over anhydrous calcium sulfate *in vacuo* were quantitative when molar ratios of ethylene oxide to sucrose up to 4:1 were used. When the molar ratio was 11:1, the

³ Resinous Products and Chemical Co.

crude yield was 92.5%, indicating 87% conversion of ethylene oxide to non-volatile products.

The reaction products were obtained by concentrating their solutions, prepared as above, *in vacuo*, dehydrating by distillation of the residues with five volumes of dioxane or pyridine, and removing the solvent *in vacuo*. The resulting gums could not be crystallized although many attempts were made using various solvents. One crystalline substance was obtained as follows: The dehydrated product from 17.6 g. of ethylene oxide (0.4 mole) and 34.3 g. of sucrose (0.1 mole) was dissolved in hot dioxane and cooled. The gum (6.5 g.) which separated was dissolved in 6 g. of methanol and seeded with crystals which had appeared spontaneously in a sample of the original crude addition product. After a few hours, there was filtered off 1.3 g. of white needles, m.p. 205–207°. After recrystallization from methanol, the melting point was 215°; $[\alpha]_D^{25} -38.7^\circ$ (0.295 g., made up to 10 ml. with water, gave $\alpha_D^{25} = -1.14^\circ$, 1 dm. tube).

Anal. Calc'd for $C_{12}H_{22}O_{11} \cdot 2C_2H_4O$: C, 44.7; H, 7.02.

Found: C, 44.8; H, 6.79.

Chemical properties of addition products

Inversion. Neutralized reaction mixtures of one and two moles of ethylene oxide per mole of sucrose and a sucrose solution of the same concentration as that in the reaction

TABLE I
SAPONIFICATION EQUIVALENTS OF ACETYLATED ADDITION PRODUCTS

MOLAR RATIO OF ETHYLENE OXIDE TO SUCROSE ^a	EQUIVALENT WEIGHT, CALC'D FOR OCTAACETATE	FOUND
1	90.45	90.9
2	96.0	96.8
3	101.45	100.7
4	107.0	103.8

^a Proportions of reactants used to make the addition product.

products were each made 0.1 *N* in hydrochloric acid by adding standard acid to equal volumes of the solutions. The molar ratios of ethylene oxide to sucrose and the initial and final observed rotations (Na_D line, 1 dm. tube, 25°) were: 0:1, +10.7°, -3.2°; 1:1, +10.4°, -2.0°; 2:1, +10.2°, -1.1°.

Reaction with acetic anhydride. Addition products prepared from 0.01 mole of sucrose and dehydrated by distilling with pyridine were treated with 25 ml. of acetic anhydride and heated on a boiling water-bath for three hours. After the acetic acid and anhydride were distilled off *in vacuo*, the residual oils were taken up in ethyl ether, washed first with 10% sodium carbonate solution, and then to neutrality with water. The ether layers were dried over anhydrous calcium sulfate and evaporated to give colorless, viscous oils, yields 4.5–5.5 g. The acetates were insoluble in water, soluble in methanol, ethanol, chloroform, and ethyl ether. Their saponification equivalents, determined by refluxing for one hour with excess 1 *N* sodium hydroxide in 95% ethanol and titrating the excess alkali, are shown in Table I.

Reaction with phenylhydrazine. Aqueous solutions of sucrose and of addition products each containing 1.0 g. of equivalent sucrose in 7.0 ml. were made 0.1 *N* in hydrochloric acid and warmed at 50° for two hours. To each was added a solution of 1.25 g. of phenylhydrazine hydrochloride and 1.5 g. of anhydrous sodium acetate in 10 ml. of water. The solutions were heated on a boiling water-bath. Their behavior was: sucrose, precipitation in

⁴ Microanalysis by Oakwold Laboratories, Arlington, Va.

five minutes; 1:1 addition product, precipitation in 10 minutes; 2:1 addition product, precipitation in 15 minutes; 3:1 addition product, turbidity in 30 minutes, precipitation of orange-red oil on cooling. The sucrose solution yielded 1.2 g. of D-glucose phenylosazone, m.p. 208°; the 1:1 addition product, 0.9 g. of impure D-glucose phenylosazone, m.p. 197°, mixed melting point, 203°; the 2:1 addition product, 0.9 g. of crystals contaminated with oily material, recrystallization of which gave 0.4 g. of D-glucose phenylosazone. From the 3:1 and higher addition products no crystalline osazones could be isolated.

We wish to express our gratitude to the Sugar Research Foundation for a grant in support of this work.

SUMMARY

1. Ethylene oxide was found to react with sucrose in aqueous alkaline solution at room temperature.
2. The products were gums which could not be separated into their components. These gums are considered to be mixtures of hydroxyethyl ethers of sucrose. They were hygroscopic and had little surface activity.
3. One crystalline product was isolated. Its composition indicated it to be a bis-(hydroxyethyl)sucrose.

CHATTANOOGA, TENN.

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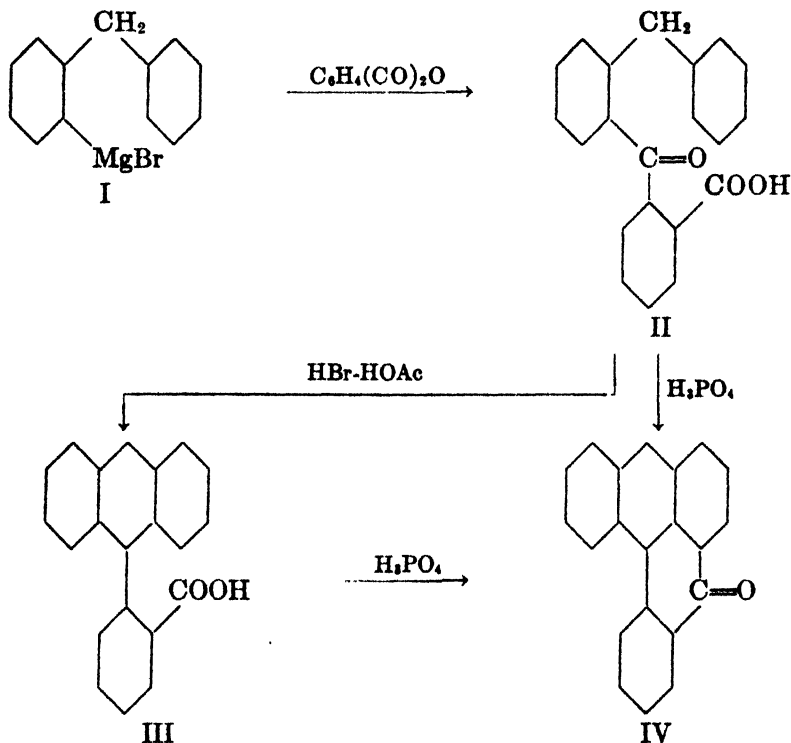
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AROMATIC CYCLODEHYDRATION. XXI. *ortho*- AND *para*-(9-ANTHRYL)BENZOIC ACIDS¹

CHARLES K. BRADSHER AND FRANK A. VINGIELLO

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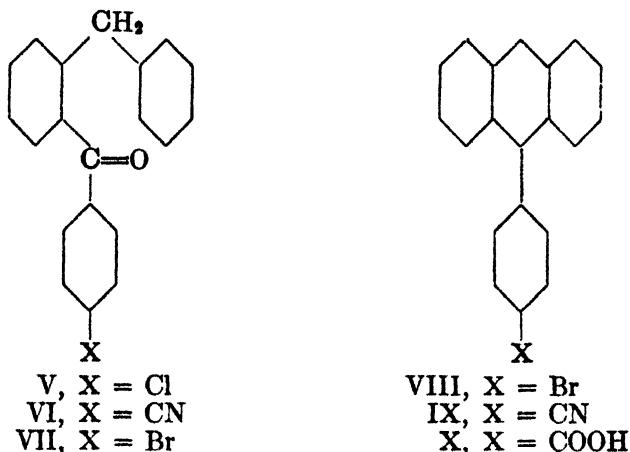
With the exception of a single complex example, the cyclization of 1-(diphenylmethyl)anthraquinone described by Scholl and Donat (1), the *o*-benzylphenone cyclization appears to have been applied only to the synthesis of hydrocarbons (2). Our present communication describes the preparation of *ortho*- and *para*-(9-anthryl)benzoic acids by this reaction. One of the acids, the *ortho* (III), has been prepared previously by Cook (3) and by Scholl and Donat (1) through reduction of the lactone of 9-hydroxy-9-(*o*-carboxyphenyl)anthrone.



In the present work, the Grignard reagent (I) prepared from 2-bromodiphenylmethane was allowed to react with phthalic anhydride to yield 2-benzylphenone-2'-carboxylic acid (II). This compound underwent cyclodehydration readily to yield the expected *o*-(9-anthryl)benzoic acid (III). From the structure of this acid, it might be predicted that it could be cyclized to coeranthrone (IV). Scholl and Donat (1) attempted this ring closure using warm

¹ For the preceding communication of this series see Bradsher, Rapoport, and Anderson, *J. Am. Chem. Soc.*, **68**, 2152 (1946).

concentrated sulfuric acid but obtained only very impure dirty-red coeranthrone (IV). Our experiments with the same reagent were no more promising, and it appeared that sulfur dioxide was being given off in the reaction. When *o*-(9-anthryl)benzoic acid (III) was heated at 195° with the less strongly oxidizing phosphoric acid, it was found that cyclization to coeranthrone could be effected in 47% yield. A mixture of phosphoric acid and phosphorus pentoxide was used to bring about the elimination of two moles of water from 2-benzylbenzophenone-2'-carboxylic acid (II), giving a 66% yield of coeranthrone.



The *p*-(9-anthryl)benzoic acid (X) was prepared in two ways. In the first, 2-benzyl-4'-chlorobenzophenone (V) was prepared by the reaction of *p*-chlorophenylmagnesium iodide with *o*-benzylbenzonitrile and converted to the corresponding nitrile (VI) by the action of cuprous cyanide. Cyclization of this keto-nitrile was accompanied by hydrolysis, yielding the free acid (X).

In the alternate procedure, 9-(*p*-bromophenyl)anthracene (VIII) was prepared by the *o*-benzylphenone cyclization and converted to the nitrile (IX) which, on hydrolysis, gave the expected acid (X).

EXPERIMENTAL

***o*-Bromodiphenylmethane.** It was found that this halide could be prepared in better yield when *o*-bromobenzophenone was reduced by the action of hydriodic acid rather than by the Clemmensen reduction employed previously (4, 5). A mixture of 10 g. of *o*-bromobenzophenone, 10 ml. of 47% hydriodic acid, and 10 g. of red phosphorus was refluxed and stirred for forty hours. After neutralization, the mixture was extracted with ether. The ethereal extract was filtered, dried, and concentrated. The residue was fractionated under reduced pressure, yielding 9.5 g. (82%) of colorless liquid, b.p. 179–183° (21.5 mm.) [Lit. (5) 175° (22 mm.)].

2-Benzylbenzophenone-2'-carboxylic acid (II). A Grignard reagent prepared in ether from 18 g. of *o*-bromodiphenylmethane was transferred slowly under nitrogen pressure to a stirred boiling solution containing 9.8 g. of phthalic anhydride in 200 ml. of anhydrous benzene. The mixture was stirred and refluxed for two hours and then allowed to stand overnight. After decomposition in the usual way, the benzene solution was extracted twice with sodium carbonate solution. Careful acidification of the carbonate extract gave a pale yellow precipitate which, once recrystallized from benzene, gave 14.3 g. (68%) of

fine white needles, m.p. 170–171°. An analytical sample was obtained by repeated recrystallization, m.p. 172–174°.

Anal. Calc'd for $C_{21}H_{16}O_2$: C, 79.73; H, 5.10.

Found: C, 79.80; H, 5.30.

o-(9-Anthryl)benzoic acid (III). A solution of 0.5 g. of the above keto-acid (II) was refluxed for twenty hours in a mixture containing 4 ml. of 48% hydrobromic acid, 1 ml. of water, and 15 ml. of acetic acid. The mixture was cooled and the crystalline product collected, m.p. 238–242°; yield 0.38 g. (81%). It was twice recrystallized from ethanol, m.p. 242–243° [Lit. (1) 242–243.5°].

Anal. Calc'd for $C_{21}H_{14}O_2$: C, 84.55; H, 4.73.

Found: C, 84.36; H, 4.63.

The methyl ester was prepared by the action of diazomethane, m.p. 156–157°.

Anal. Calc'd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16.

Found: C, 84.59; H, 5.53.

Coeranthrone (IV). (a) *By cyclization of o*-(9-anthryl)benzoic acid (III). A mixture consisting of 0.35 g. of the acid (III) and 20 ml. of 85% phosphoric acid was heated for two and one-half hours in an oil-bath at 195°. The red solution was poured on ice and the red product collected and recrystallized from acetic acid as dark red needles, m.p. 177–178.5° [Lit. (1) 178°]; yield 0.15 g. (47%).

(b) *By cyclization of 2-benzylbenzophenone-2'-carboxylic acid* (II). To a mixture of 0.5 g. of the keto-acid (II) and 5 ml. of phosphoric acid, phosphorus pentoxide was added until the mixture had a pasty consistency. It was then heated at 190–200° for one and three-quarters hours and at 250° for an additional quarter hour. On decomposition with ice-water, a brick-red precipitate was obtained. This was collected and boiled with ammonium hydroxide to remove unchanged acid, then collected and recrystallized from acetic acid as flat, dark, red-brown needles, m.p. 178–180°, yield 0.29 g. (66%). This product gave no depression of melting point when mixed with that obtained with (a).

2-Benzyl-4'-chlorobenzophenone (V). A Grignard reagent was prepared from 37 g. of *p*-chloriodobenzene, and after removal of most of the ether, a solution of 10 g. of *o*-benzylbenzonitrile was added. The mixture was refluxed for fourteen hours, cooled, and decomposed with 20% ammonium chloride solution. The benzene layer was separated and refluxed with 200 ml. of 2 *N* hydrochloric acid for ten hours. The organic layer was separated, washed, dried, concentrated, and the residue distilled under reduced pressure. The fraction boiling at 237–239° (8 mm.) was collected. Recrystallized from ethanol (using Norit), the product was obtained as long white needles, m.p. 73°; yield 9.4 g. (59%).

Anal. Calc'd for $C_{20}H_{15}ClO$: C, 78.30; H, 4.93.

Found: C, 78.62; H, 5.31.

2-Benzyl-4'-cyanobenzophenone (VI). A mixture containing 7 g. of 2-benzyl-4'-chlorobenzophenone, 4.1 g. of cuprous cyanide, 0.01 g. of cupric sulfate, and 10 ml. of pyridine was heated in an oil-bath at 250° for fifteen hours, the pyridine being allowed to escape. At the end of this period, the mixture was cooled and poured into dilute ammonium hydroxide solution, extracted with benzene, the benzene extract concentrated, and the residue distilled under reduced pressure. The distillate was recrystallized several times from ethyl alcohol (using Norit), as long white needles, m.p. 104.5–105°; yield 1.8 g. (27%).

Anal. Calc'd for $C_{21}H_{15}NO$: C, 84.83; H, 5.09; N, 4.71

Found: C, 84.62; H, 5.02; N, 4.80.

2-Benzyl-4'-bromobenzophenone (VII). A Grignard reagent prepared from 24.7 g. of *o*-bromodiphenylmethane was added dropwise with stirring to a solution of 20 g. of *p*-bromobenzoyl chloride in 400 ml. of anhydrous benzene heated to 45°. After addition was complete, the mixture was refluxed for two hours, during which most of the ether was allowed to escape. After standing overnight, the mixture was decomposed, the benzene layer separated, washed, concentrated, and the residue fractionated under reduced pressure. The portion boiling at 210–220° (1 mm.) solidified on standing, yield 16 g. (50%). Recrystallization from ethanol yielded white plates, m.p. 83–84.5°.

THE PREPARATION AND CONDENSATION POLYMERIZATION OF HIGHER ALKYL ESTERS OF α -AMINO ACIDS¹

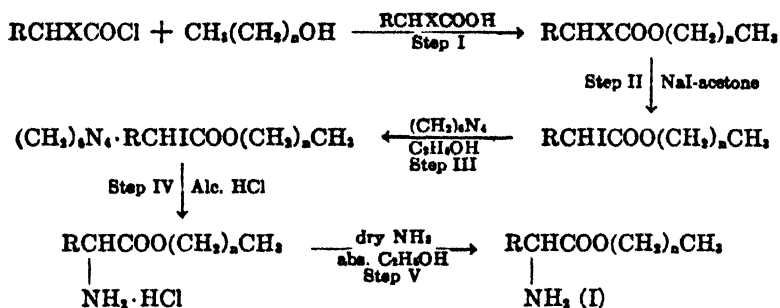
ABRAHAM BANIEL, MAX FRANKEL, ISRAEL FRIEDRICH,
AND AHARON KATCHALSKY

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In the course of our general research program on the polymerization of α -amino acid derivatives (1, 2, 3, 4, 4a, 5), we have observed (6, cf. refs. 1, 3) that surface forces enhanced the velocity of the condensation polymerization which results in polypeptide chains (1, 7), even with fairly stable amino acid esters. This observation has prompted us to investigate whether the surface activity of higher alkyl esters of α -amino acids would similarly enhance the velocity of polymerization of such esters, in comparison with that of the lower alkyl esters.

The preparation of a series of esters of general formula (I) was carried out according to the following general scheme, advantageously adapting the hexamethylenetetramine method of Delépine (8), Mannich and Drauzburg (9) and Galat and Elion (10).

Synthetic Scheme:—



R = H or CH₃; X = Cl or Br; n = 7, 11, 15 or 17. Yields at each step were 80–90%, with an over-all yield of amino acid esters of about 60%.

The same procedure was successfully applied to the preparation of β -naphthyl α -aminoacetate and the previously known cholesteryl α -aminoacetate (11).

As anticipated, the new esters polymerized readily, with elimination of the free alcohol and formation of polypeptide linkages.

EXPERIMENTAL

Step I. Preparation of RCHXCOO(CH₂)_nCH₃. The alcohol to be esterified, mixed with three to four parts by weight of RCHXCOOH, was refluxed with 1.5 equivalents of the corresponding acid chloride until evolution of hydrogen chloride was complete, usually about two hours. The ester was precipitated by pouring the hot reaction mixture, slowly, into a large volume of vigorously stirred ice-water, and was then allowed to stand for 2–3

¹ Abstracted from dissertations for the M. Sc. degree of A. Baniel (1943) and I. Friedrich (1947) at the Hebrew University.

hours to complete hydrolysis of the excess acid chloride and solution of the acid. The crude ester was taken into ether and the ether solution freed of acid by washing with sodium bicarbonate solution, washed to neutrality with water, and dried over sodium sulfate. The ester was isolated by concentration of the ether solution and purified by distillation *in vacuo*. The properties and analytical data for these esters are given in Table I.

Step II. Preparation of $RCHICOO(CH_2)_nCH_3$. The chloro- or bromo-ester was treated for two hours in the dark with an anhydrous acetone solution of 1.25 equivalents of sodium iodide. The solution was freed of the separated salt by filtration and concentrated on the steam-bath. The residue was extracted with peroxide-free ether, the ether solution was washed free of traces of iodine with aqueous sodium bisulfite and then with water. The ether solution, dried over sodium sulfate, was concentrated on the steam-bath and the

TABLE I
 $RCHXCOO(CH_2)_nCH_3$

ESTER			FORMULA	ANAL., % X.		M.P., °C.	B.P., °C/MM.
R	X	n		Calc'd	Found		
H	Cl	7	$C_{10}H_{19}ClO_2$	17.2	17.2	Liqu.	110/2
H	Cl	11	$C_{14}H_{27}ClO_2$	13.5	13.6	7	190/25
H	Cl	15	$C_{18}H_{33}ClO_2$	11.1	11.2	28	180/2
H	Cl	17	$C_{20}H_{35}ClO_2$	10.2	10.3	29	Dec.
CH_3	Br	7	$C_{11}H_{21}BrO_2$	30.2	30.1	Liqu.	130/2
CH_3	Br	15	$C_{19}H_{37}BrO_2$	21.2	21.8	11	220/2

TABLE II
 $RCHICOO(CH_2)_nCH_3$

ESTER		FORMULA	IODINE, %		M.P., °C.	B.P., °C/2MM.
R	n		Calc'd	Found		
H	7	$C_{10}H_{19}IO_2$	42.7	43.9	Liqu.	122
H	11	$C_{14}H_{27}IO_2$	35.9	36.3	6	173
H	15	$C_{18}H_{33}IO_2$	31.0	30.2	14	201
H	17	$C_{20}H_{35}IO_2$	29.0	28.6	15	Dec.
CH_3	7	$C_{11}H_{21}IO_2$	40.7	39.3	Liqu.	132
CH_3	15	$C_{19}H_{37}IO_2$	29.9	29.2	29	230

iodo-acid ester was purified by distillation *in vacuo*. The properties and analytical data for the iodo-acid esters are given in Table II.

The iodo-acid esters are unstable, undergoing slight decomposition during distillation, as well as on standing for any length of time, as evidenced by the appearance of free iodine. For this reason analyses were always performed immediately on the freshly distilled product.

Step III. Preparation of $(CH_2)_6N_4 \cdot RCHICOO(CH_2)_nCH_3$. The iodo-acid ester (1.5 moles) was added to a warm solution of one mole of hexamethylenetetramine in 500 ml. of alcohol and boiled under reflux for thirty minutes. The mixture was allowed to stand overnight, during which some product separated. The reaction mixture was poured into five liters of vigorously stirred water, completing the precipitation of the product and dissolving the unreacted hexamethylenetetramine. The product was filtered only after it had remained in contact with the aqueous solution for an additional 24 hours, to ensure

complete solution of hexamethylenetetramine and permit the original, finely divided, flaky precipitate to grow into coarser, more easily filterable aggregates. The product was then separated, washed with distilled water, and dried in a desiccator.

For the preparation of the octyl esters ($n = 7$) the procedure was modified to achieve improved yields by mixing one mole of the iodo-acid ester with 1.25 moles of the tetramine in hot alcohol, and allowing the mixture to stand for a week before working up. The product was isolated, in these cases, by evaporation of the alcohol *in vacuo*, the residue washed with water and dried *in vacuo*. The dried residue was freed of unreacted ester by washing with absolute ether and again drying in a desiccator. The product was then obtained as a white or slightly yellow crystalline powder. The properties and analytical data for these complexes are listed in Table III.

Step IV. Preparation of salts of $RCH(NH_2)_nCH_3$. Two grams of the tetramine complex was suspended in 10 ml. of absolute alcohol. Four equivalents of concentrated hydrochloric acid was added to the mixture which was then boiled gently under reflux for 20–30 minutes.

It was necessary to apply different techniques of isolation for those esters in which $n = 7$ or 9 than for those in which $n = 11, 15$, or 17. In the former cases the salts are too water-soluble to be isolated as readily as the corresponding salts of the latter group.

TABLE III
(CH_2)₆N₄·RCHICOO(CH_2)_nCH₃

ESTER		M.P., °C.	FORMULA	IODINE, %		NITROGEN, %	
R	n			Calc'd	Found	Calc'd	Found
H	7	173	C ₁₆ H ₃₁ IN ₄ O ₂	28.9	28.1	12.8	13.5*
H	11	175	C ₂₆ H ₅₁ IN ₄ O ₂	25.7	26.0	11.3	11.4
H	15	108	C ₃₆ H ₆₇ IN ₄ O ₂	23.1	23.1	10.2	10.4
H	17	104	C ₃₈ H ₇₁ IN ₄ O ₂	22.0	21.3	9.7	9.6
CH ₃	7	179	C ₁₇ H ₃₃ IN ₄ O ₂	28.8	27.5	12.7	12.9
CH ₃	15	112	C ₂₅ H ₄₉ IN ₄ O ₂	22.5	22.4	9.9	10.1

* The material is slightly contaminated by (CH_2)₆N₄.

(a) For $n = 11, 15$, or 17. The hot alcoholic solution of the hydrochloride was poured slowly, with vigorous stirring, into a concentrated solution of sodium bisulfite. The bisulfite salt separated at once as a flaky, white precipitate which was separated by filtration, after standing for two hours, and dried in a desiccator. The salt was recrystallized from absolute ethanol, and was used in this form for the liberation of the free amino acid ester.

(b) For $n = 7$ or 9. The hydrolysis mixture was concentrated in a desiccator over solid sodium hydroxide to a syrup, which was used in the following step without further purification.

Step V. Liberation of $RCH(NH_2)COO(CH_2)_nCH_3$ from their salts. Either salt (IVa or IVb) was suspended in dry ether, the mixture cooled, and then treated with a slow stream of dry gaseous ammonia under strictly anhydrous conditions. A large excess and a rapid stream of ammonia should be avoided to prevent loss of lower esters by volatilization.

After filtration, the ether solution was concentrated in a vacuum desiccator. In this manner the ester was isolated analytically pure. All the esters were colorless liquids or white, soft, waxy solids which tended to polymerize on standing. However, they could be stored as stable hydrochlorides. The properties and analytical data for the esters are given in Table IV.

Preparation of pure hydrochlorides of the two cetyl esters ($n = 15$, $R = H$ or CH_3) was achieved by treatment of an ether solution of each ester with dry gaseous hydrogen chloride.

The crystalline hydrochlorides, which separate immediately, were filtered and dried for analysis *in vacuo* over sodium hydroxide.

Cetyl α -aminoacetate hydrochloride:

Anal. Calc'd for $C_{18}H_{35}ClNO_2$: Cl, 10.6; N, 4.2.

Found: Cl, 10.4; N, 4.2.

Cetyl α -aminopropionate hydrochloride:

Anal. Calc'd for $C_{19}H_{40}ClNO_2$: Cl, 10.2; N, 4.0.

Found: Cl, 10.3; N, 3.9.

β -Naphthyl α -aminoacetate. The present method has been successfully applied to the synthesis of phenolic esters of α -amino acids by Mannich and Drauzburg (9) and Lakner (12). Using β -naphthyl α -chloroacetate (13) as starting material, and following the modifications of the outlined synthetic scheme for the higher alkyl esters, β -naphthyl α -aminoacetate was produced. The yield at each step was 80–90%. It was obtained as a solid, m.p. 60°.

Anal. Calc'd for $C_{13}H_{11}NO_2$: N, 7.0. Found: N, 6.8.

The hydrochloride was obtained as a solid, m.p. 224° (dec.).

Anal. Calc'd for $C_{13}H_{12}ClNO_2$: Cl, 14.9. Found: Cl, 14.6.

Cholesteryl α -aminoacetate. This ester has been prepared (11) from cholesterol and aminoacetyl chloride. Using cholesteryl α -chloroacetate (14) in our synthetic scheme, cholesteryl α -aminoacetate, identical with that previously reported (11), was obtained.

TABLE IV
 $RCH(NH_2)COO(CH_2)_nCH_3$

ESTER		M.P., °C.	FORMULA	NITROGEN, %	
R	n			Calc'd	Found
H	7	Liqu.	$C_{10}H_{21}NO_2$	7.5	7.4
H	15	52	$C_{18}H_{37}NO_2$	4.7	4.4
H	17	60	$C_{20}H_{41}NO_2$	4.3	4.3
CH_3	7	Liqu.	$C_{11}H_{23}NO_2$	7.0	6.9
CH_3	15	57	$C_{19}H_{39}NO_2$	4.5	4.2

Polymerization experiments. (A) *Surface polymerization.* We wish to describe only some preliminary observations. Monolayers of the α -aminoacetates, including cetyl and octadecyl, were spread on a water surface and the thus formed films were immediately deposited on a polished metal plate by Blodgett's technique (15). In carrying out similar experiments with the lower alkyl esters of glycine and alanine, it was found that the major part dissolved in water but the remainder formed an insoluble film. The deposit of polymer was scraped off and submitted to the biuret test. A very distinct violet color, indicative of the presence of polypeptide linkages, was obtained. In contrast, it should be noted, the ester *per se* in bulk, at the same temperature for the same time, underwent no significant polymerization. Even methyl α -aminopropionate, which shows only very slight tendency to polymerize at room temperature, undergoes polymerization when spread and multilayered.

(B) *Heat polymerization.* Cetyl α -aminoacetate was heated at 80° in a sealed tube for two hours. The molten mass solidified slowly at the end of the heating period. The contents of the tube was cooled and washed with ether to extract unchanged monomer and cetyl alcohol. Van Slyke manometric analyses for free amino groups proved that condensation-polymerization had occurred. A polyglycine ester with an average of twenty glycine units per polymer was obtained.

In contrast to the polymerization of the lower alkyl esters, the formation of diketopiperazine was not observed in this experiment.

SUMMARY

A method for the preparation of higher alkyl esters of glycine and alanine is described. The preparation and properties of the octyl, dodecyl, hexadecyl, octadecyl, β -naphthyl, and cholesteryl esters of these amino acids, as well as the intermediates are described.

Results of preliminary experiments on the surface enhanced condensation-polymerization of various esters of glycine and alanine are reported.

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DERIVATIVES OF SALICYLIC ACID

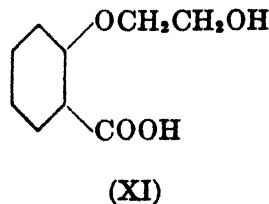
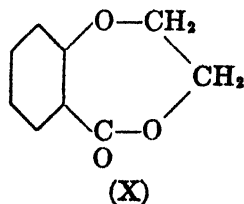
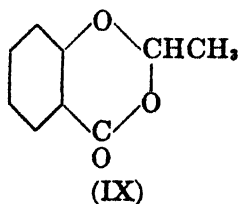
CH. WEIZMANN, ERNST D. BERGMANN, AND M. SULZBACHER

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In the hope that the combination of the aspirin and the phenacetin structures in one molecule may give rise to pharmacologically interesting substances, older preparative experiments in the series of *N*-salicyl-*p*-aminophenol (I) (III) were repeated and extended. [Salicyl phenetidine (I) has been described by Bolezzi (1b) and by Cohn (1a), and also by Cohn (2), Anschütz (3), and in a U. S. Patent (4).] The results of this investigation are summarized in Charts A and B.

Some of the observations made are believed to be of interest. The hydroxyl groups of (I) and (III) are converted into the corresponding carbonates (IIa and VIII) by treatment with methyl chloroformate in pyridine and under fairly mild conditions. [This type of reaction is, of course, not new (5).] Salol reacts with *p*-aminophenol in an unsatisfactory manner, but using a diluent such as 1,2,4-trichlorobenzene or 1-methylnaphthalene (6), VanAllan (1d) reported good results. Acetylsalicyl chloride, too, reacts smoothly with *p*-aminophenol, and IV can, therefore, be prepared easily by hydrolysis of its diacetyl and its two monoacetyl derivatives. Acetylation of IV attacks first the hydroxyl group of the *p*-aminophenol radical (VI), so that the isomeric monoacetyl compound (III) is only accessible by the condensation of acetylsalicyl chloride with *p*-aminophenol.

In connection with these experiments, β -hydroxyethyl salicylate, $\text{HOCH}_2\text{CH}_2\text{COOCH}_2\text{CH}_2\text{OH}$, was prepared from sodium salicylate and ethylene chlorohydrin.¹ As by-product, a crystalline compound was observed (m.p. 82°) which gave analysis for $\text{C}_8\text{H}_8\text{O}_3$. Its melting point excluded the possibility that it was 2-methyl-4-keto-1,3-benzodioxane (IX) which has recently been described as melting at 33° (7). We assume, therefore, that the substance is the seven-membered cyclic ether (X) of the ester. It could also have formed through *o*-(β -hydroxyethoxy)benzoic acid (XI).



EXPERIMENTAL

Acetylsalicyl phenetidine (II). To a solution of 514 g. (2 moles) of salicyl phenetidine (from alcohol, m.p. 146°) in 790 cc. of pyridine, 188 g. of acetyl chloride was gradually added

¹ See *Chem. Zentr.*, 1906, II, 934. The reaction of ethylene chlorohydrin with sodium salts of organic acids has been studied before in only one other case, that of benzoic acid (*Chem. Zentr.*, 1912, I, 1407). We have investigated its reaction with sodium propionate, cinnamate, and phenyleinchonate; they all give easily β -hydroxyethyl esters.

CHART A

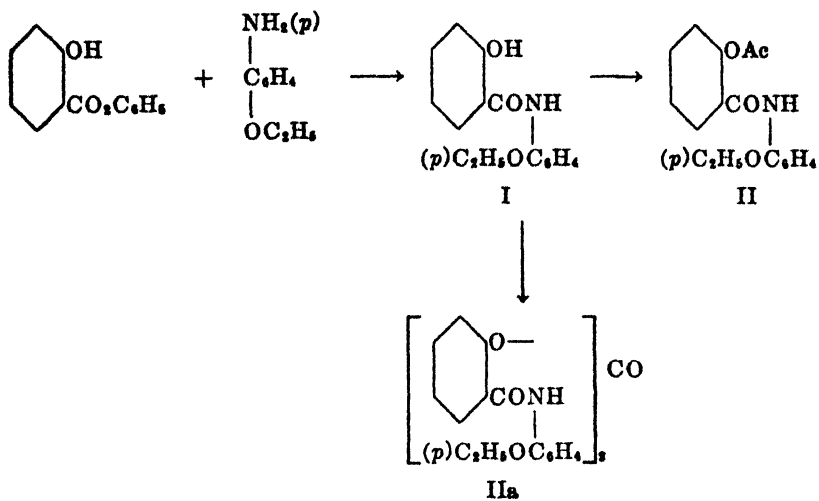
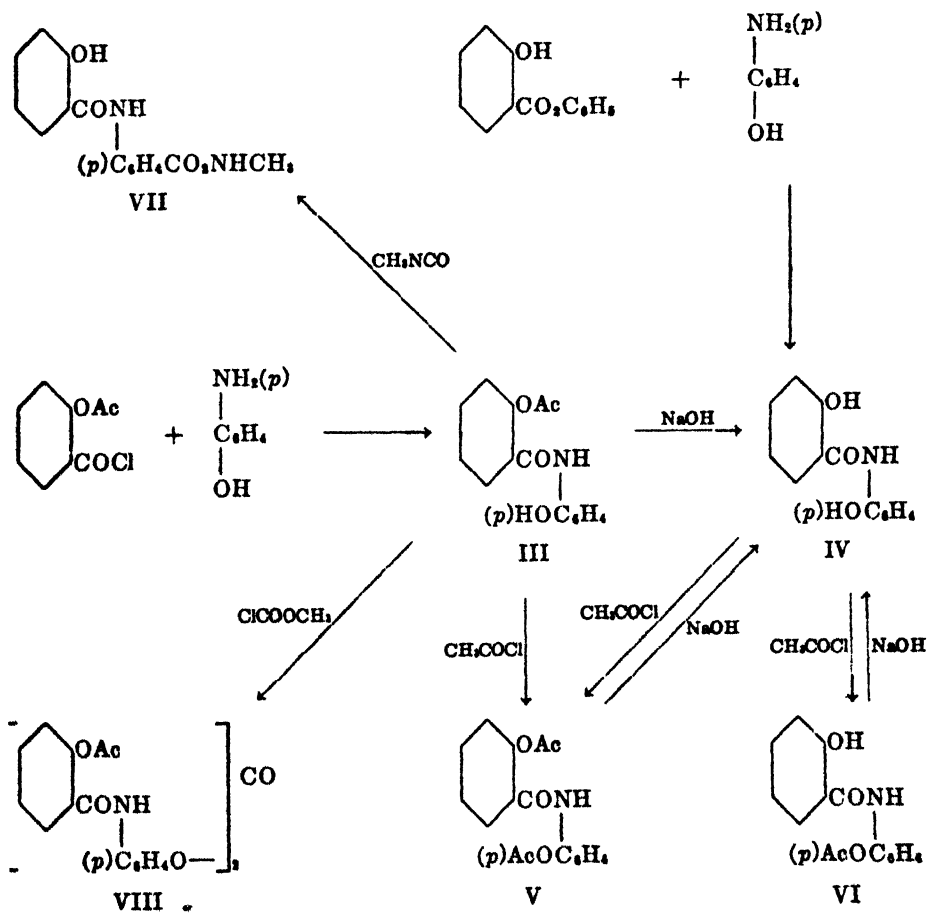


CHART B



in the course of two hours with cooling (0°) and stirring. The stirring was continued for two hours, and the reaction completed by refluxing for one hour. Dilute sulfuric acid precipitated the product, which was recrystallized from acetone or butyl acetate, and melted at 134°; yield 545 g. (91%).

Anal. Calc'd for $C_{17}H_{17}NO_4$: C, 68.2; H, 5.7; N, 4.7.

Found: C, 68.0; H, 5.8; N, 4.5.

Acetylation with acetyl chloride and acetic anhydride at 100° led, by displacement of the acetylsalicyl radical, to phenacetin (from butyl acetate, m.p. 134°), which depressed the m.p. of II considerably.

Carbonate of salicyl phenetide (IIa). Methyl chloroformate (1.1 cc.) in chloroform (5 cc.) reacted with salicyl phenetide (2.6 g.) in pyridine (10 cc.) with liberation of heat. After twenty-four hours at room temperature, the mixture was heated at 100° for one hour and poured into dilute sulfuric acid. The product which separated was recrystallized from pyridine, and formed aggregates of fine prisms, which melted at 256–257°.

Anal. Calc'd for $C_{21}H_{23}N_2O_7$: C, 68.9; H, 5.2; N, 5.2.

Found: C, 68.9; H, 5.0; N, 5.4.

For the synthesis of *N-acetylsalicyl-p-aminophenol (III)*, the following method has proved satisfactory: (a) The chloride of acetylsalicylic acid was best prepared (8) by adding the free acid (720 g., 4 moles) to a solution of thionyl chloride (952 g., 8 moles) in benzene (1300 cc.) and refluxing the mixture for six hours. The volatile components of the product were removed by distillation and finally by heating at 110° under 15 mm. pressure for about two hours. Upon cooling, the oil crystallized spontaneously. It did not require further purification, e.g., by distillation (b.p. 135°/12 mm.; 99°/3.5 mm.); m.p. 43–44°; yield 745 g. (94%).

(b) A solution of 397 g. (2 moles) of the chloride in 600 cc. of ether was added at 0° to the vigorously stirred suspension of 436 g. (4 moles) of *p*-aminophenol in 1400 cc. of anhydrous ether. The reaction was completed by continuing the stirring at room temperature (two hours) and finally at the boiling point of ether (three hours). The solid product was filtered, dried, digested with water, and subsequently with very dilute hydrochloric acid, and washed chloride-free. (The mother liquor contained the excess of aminophenol, which could be recovered in the normal way by use of sodium sulfite.) From butyl acetate, the product crystallized in glistening needles, m.p. 167°; yield 490 g. (90%).

Anal. Calc'd for $C_{15}H_{13}N_2O_2$: N, 5.2. Found: N, 5.1, 5.2.

The carbonate (VIII) of (III) was prepared as described for the salicyl phenetide (IIa). After recrystallization from a mixture of equal volumes of benzene and light petroleum, it formed fine needles, melting at 134–135°.

Anal. Calc'd for $C_{21}H_{23}N_2O_9$: N, 4.9. Found: N, 4.6.

N-Salicylaminophenol (IV). (a) The *N*-acetylsalicyl compound (III) was hydrolyzed when dissolved in cold 0.1 *N* NaOH solution and kept at room temperature for five minutes. Addition of 0.1 *N* HCl precipitated the desired compound in quantitative yield. From very dilute alcohol or xylene, it crystallized in needles of m.p. 178°. Ferric chloride solution gave a purple color reaction; the solution of the substance in aqueous ammonia turned blue on exposure to air.

(b) The reaction of salol (125 g.) and *p*-aminophenol (22 g.) at 200° (one hour) gave a resinous product which crystallized upon trituration with acetone (50 cc.), but could be purified only with some difficulty. Acetylation of the crude product with boiling acetic anhydride and anhydrous sodium acetate, however, gave the pure diacetyl derivative of m.p. 151° (see below). Method (a) is preferable in our experience.

N-Acetylsalicyl-p-aminophenyl acetate (V). (a) A mixture of 54.2 g. (0.2 mole) of

N-acetylsalicyl-*p*-aminophenol (III) and 80 cc. of acetyl chloride was refluxed for four hours. The excess of the chloride was removed from the crystalline product by distillation and the residue recrystallized from alcohol. It formed colorless needles of m.p. 151°; yield 58 g. (93%).

Anal. Calc'd for $C_{17}H_{15}NO_3$: N, 4.5. Found: N, 4.4, 4.6.

(b) N-Salicyl-*p*-aminophenol (IV) was refluxed with an excess of acetyl chloride for six hours. The product was isolated in the manner described under (a).

Hydrolysis with 2 moles of aqueous 0.1 N NaOH brought the diacetyl compound (V) into solution very slowly; it produced first N-salicyl-*p*-aminophenyl acetate (VI), described presently, then N-salicyl-*p*-aminophenol (IV).

*N-Salicyl-*p*-aminophenyl acetate (VI).* Equimolecular quantities of N-salicyl-*p*-aminophenol (IV) and acetyl chloride were refluxed for two hours. The reaction product was triturated with water, dried, and recrystallized from ethyl alcohol. It formed needles, melting at 181°; yield 61%.

Anal. Calc'd for $C_{16}H_{13}NO_4$: C, 66.4; H, 4.8; N, 5.2.

Found: C, 66.1; H, 5.0; N, 5.0.

Methylurethan (VII) of N-salicylaminophenol (IV). The reaction of N-acetylsalicyl-*p*-aminophenol (III) with methyl isocyanate is accompanied by deacetylation. It was carried out by heating 3.3 g. of (III) and 2.5 g. of methyl isocyanate at 60° for 10 hours (sealed tube). The reaction product was freed from excess reagent and triturated with methanol, which left a small amount of the starting material undissolved. The solution was evaporated to dryness, and the residue recrystallized from a small quantity of propyl alcohol. The methylurethan formed aggregates of needles, m.p. 199°, which gave a positive response to ferric chloride solution.

Anal. Calc'd for $C_{15}H_{11}N_2O_2$: C, 62.9; H, 4.9; N, 9.8.

Found: C, 62.8; H, 5.1; N, 9.6, 9.9.

β -Hydroxyethyl salicylate. A mixture of 20 g. of sodium salicylate, 8 cc. of ethylene chlorohydrin, and 0.5 g. of copper-bronze was heated at 140° for four hours. The reaction product was treated with water and ether and the residue of the ethereal layer fractionated. The desired ester boiled at 166°/13 mm.; yield 12 g. (53%).

The residue crystallized upon standing. From methyl alcohol, the cyclic ether (IX) formed either leaflets or prisms (dimorphism) and melted at 82°; it has no free hydroxyl group.

Anal. Calc'd for $C_8H_6O_2$: C, 66.0; H, 5.0.

Found: C, 66.0; H, 5.2.

REHOVOT, ISRAEL

LONDON, ENGLAND

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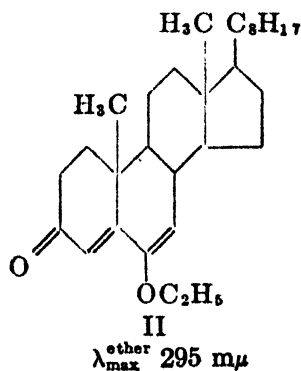
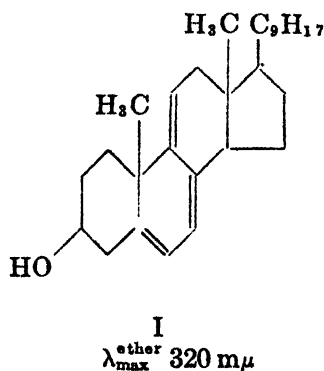
ABSORPTION SPECTROSCOPY AND THE STRUCTURES OF THE DIOSTEROLS

LOUIS F. FIESER, MARY FIESER, AND SRINIVASA RAJAGOPALAN¹*Received April 21, 1948*

The inferences that we shall present concerning the structures of two isomeric substances derived from cholesterol and characterized by marked reducing properties typical of diosphenols are based largely upon evidence of ultraviolet and infrared spectroscopy. Comparison of data for the ultraviolet region will be made in terms of a scheme developed by two of us for the calculation of the absorption maxima of steroids that constitutes a simplification and extension of those emanating from the studies of Dannenberg (1), Evans and Gillam (2), and Woodward (3). The derivation of this scheme from an analysis of data for steroids of forty-five structural types will be presented in detail in a forthcoming book;² the method itself is summarized in Table I.

A heteroannular diene is defined as one in which the two double bonds are distributed between two rings; in a homoannular diene the double bonds are contained in a single ring. In polyene systems, the effects, if any, of a change from one solvent to another or of the introduction of oxygen or halogen substituents can be neglected. The bathochromic effect of an exocyclic double bond ($5\text{ m}\mu$) is double if the linkage is exocyclic to two rings. If two chromophoric systems are present, the calculation is based on the one that absorbs at longer wavelength; thus a compound having both homo- and hetero-annular dienic systems is treated as a homoannular diene. The method of calculation is illustrated by the following examples:

Dehydroergosterol (I), $\lambda_{\text{max}} = 253 + 25$ (alkyl substitution)
 $+ 15$ (exo bonds) $+ 30$ (double bond) $= 323\text{ m}\mu$.
 Δ^4 -Cholestene-3,6-dione enol ether (II), $\lambda_{\text{max}}^{\text{ether}} = 215 + 12$
 $(\beta\text{-alkyl}) + 18$ ($\gamma\text{-OC}_2\text{H}_5$) $+ 18$ ($\delta\text{-alkyl}$) $+ 5$ (exo bond)
 $+ 30$ (double bond) $- 7$ (solvent correction) $= 291\text{ m}\mu$.



¹ Research Fellow of the National Institute of Health on leave of absence from the Haffkine Institute, Bombay.

² Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd Edition, publication in press.

TABLE I
CALCULATION OF ULTRAVIOLET ABSORPTION MAXIMA

A. HETEROANNULAR DIENES		
Parent system.....		214 m μ
Increment for each	{ Alkyl substituent.....	5
	{ Exocyclic >C=.....	5
		λ_{\max} = Total
B. HOMOANNULAR DIENES AND POLYENES		
Parent homoannular diene system.....		253 m μ
Increment for each	{ Alkyl substituent.....	5
	{ Exocyclic >C=.....	5
	{ C=C extending the conjugation....	30
		λ_{\max} = Total
C. α,β -UNSATURATED ENONES AND DIENONES*		
Parent enone		215 m μ
Increment for each substituent: R, OCOCH ₃ , OCOC ₆ H ₅ , OR, or Br	{ α	10
	{ β	12
	{ γ	18
	{ δ	18
Increment for an α -OH group.....		35
Increment for each exocyclic >C=.....		5
Increment for C=C extending the conjugation..		30
Increment for C=O extending the conjugation..		0
		$\lambda_{\max}^{\text{alc}}$ = Total

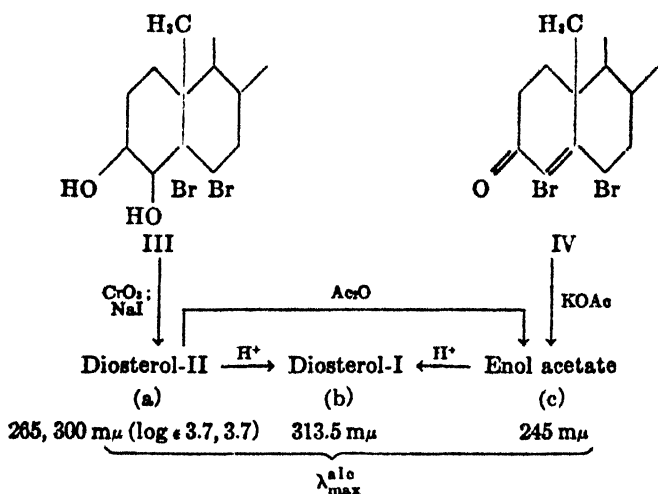
* Measurements made in solvents other than ethyl (or methyl) alcohol are corrected to this basis by the addition of the correction factors of Dannenberg (1) as follows: hexane, +11; ether, +7; dioxane, +5; chloroform, +1.

TABLE II
ABSORPTION MAXIMA

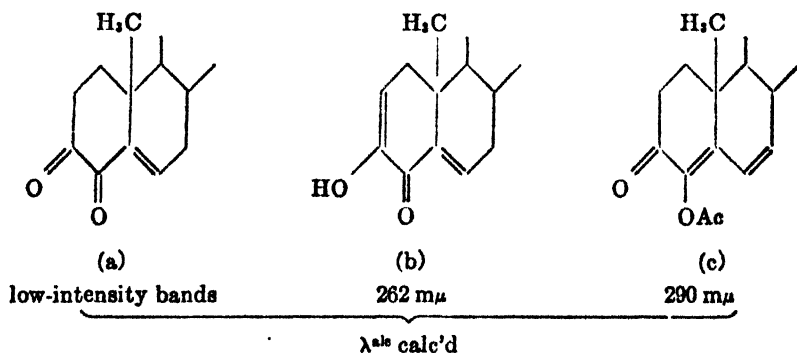
COMPOUND	$\lambda_{\max}^{\text{alc}}$ (log ϵ) (m μ)			$\lambda_{\max}^{\text{CCl}_4}$ (μ)				
				O—H	C=O		C=C	C—H
					ester	ketone		
Diosterol-I.....			313.5(3.67)	2.90		5.99	6.15	3.38
Benzoate.....	232(4.19)	287(4.41)			5.75	5.94	6.15	3.42
Diosterol-II.....		265(3.71)	300 (3.73)	2.88		5.98	6.15	3.38
Acetate (VIII).....	245(4.17)				5.72	5.96	6.14	3.45
Benzoate.....	234(4.30)				5.77	5.95	6.13	3.44

Diosterol-I was prepared by Inhoffen (4) and by Butenandt (5, 6) from cholesterol dibromide by various processes that probably proceed through 4,6-dibromo- Δ^4 -cholestenone-3 (IV) and an enol acetate obtainable from it. Petrow

and Starling (7) later prepared diosterol-II, a substance that is isomerized by acids to diosterol-I, from the intermediate III. Inhoffen ascribed to diosterol-I and the enol acetate the structures (b) and (c); Petrow and Starling concurred in this view and formulated diosterol-II as in (a). Dannenberg (1), however, pointed out that the absorption maximum at 238 $m\mu$ (ether) reported by Inhoffen for the enol acetate is not consistent with formula (c); our value found in alcoholic

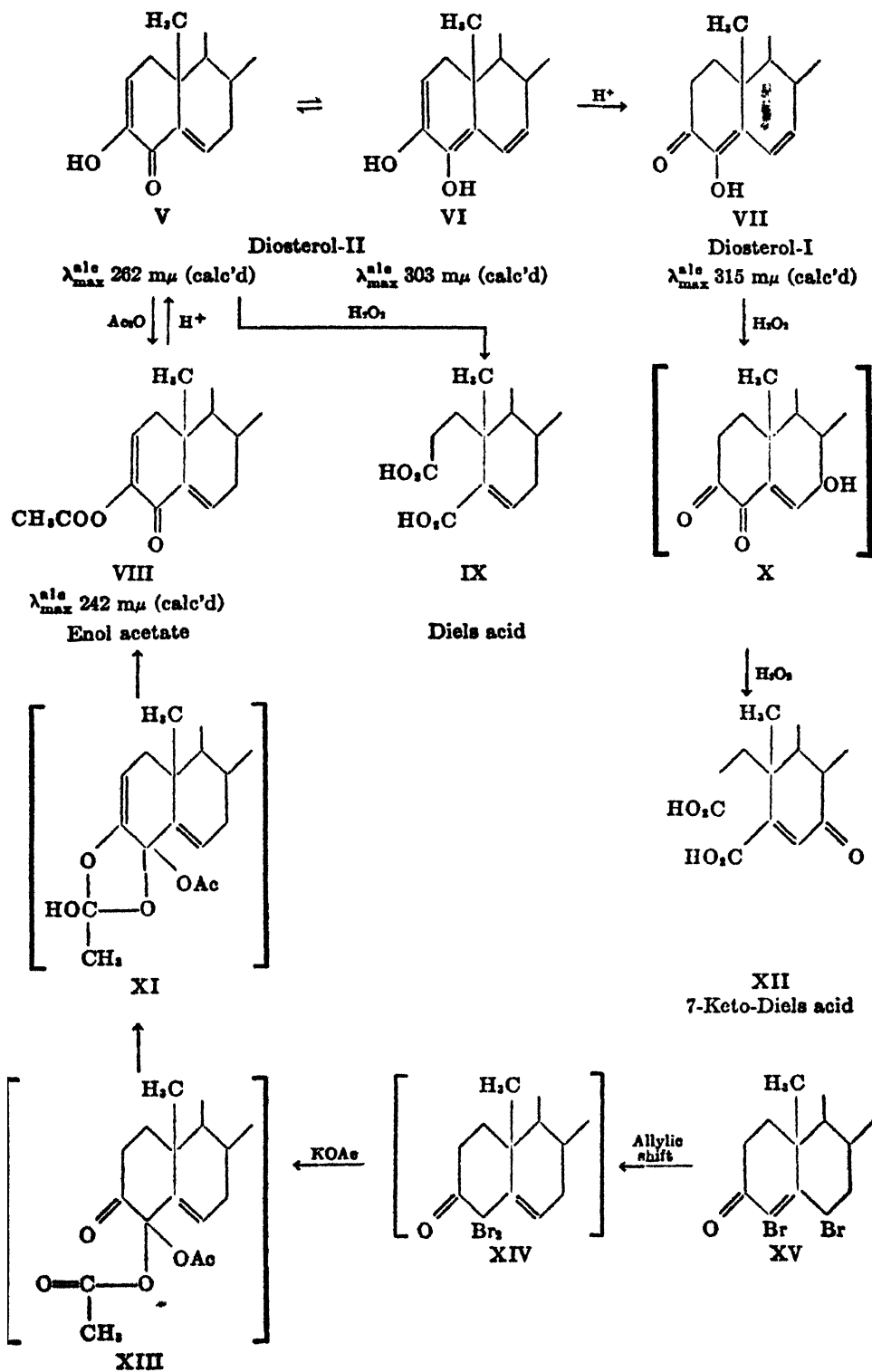


Formulas of Inhoffen, Petrow and Starling:



solution agrees with that of Inhoffen and is 45 $m\mu$ lower than the maximum calculated for (c). We may note further that the maximum found for diosterol-I, which we have checked, is much too high for the suggested structure (b). The absorption spectrum of diosterol-II has not previously been reported; a determination has now revealed that formula (a) is also in error, for the substance exhibits strong absorption at 265 $m\mu$ and 300 $m\mu$ and bears no resemblance to true α -diketones, which have two bands at higher wavelength and of extinction coefficient in the range $\log \epsilon$ 1.6–2.0 (8, 9).

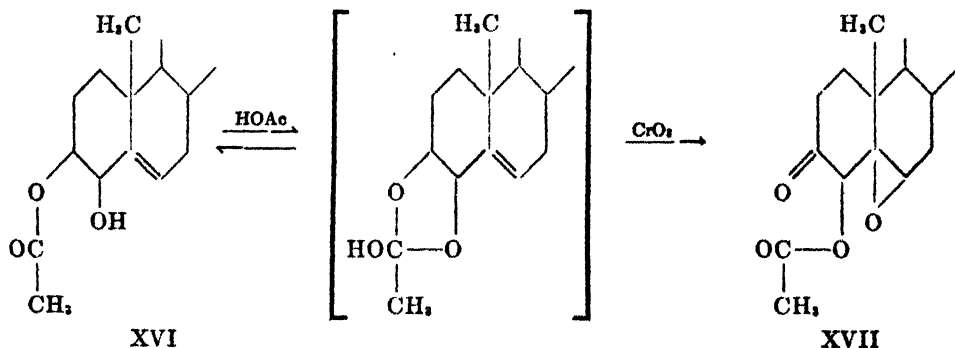
The strong band shown by diosterol-I at 313.5 $m\mu$ seemed to us suggestive of the presence of a dienolone or trienediol system, but either structure would appear inconsistent with Inhoffen's statement that the compound could not be



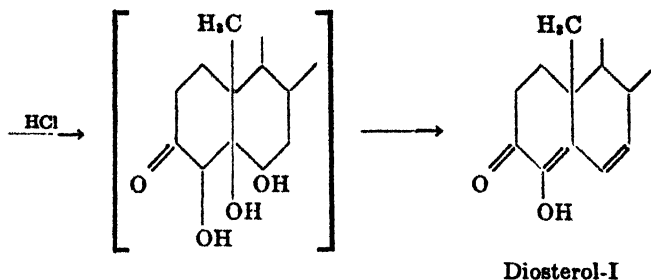
acetylated. We reinvestigated this point and found that under suitable conditions acetylation apparently can be effected, but even chromatography afforded no crystalline product. Benzoylation proved more successful and yielded a crystalline product characterized as a monobenzoate. Any possibility that the benzoate still contains an unreactive hydroxyl group was eliminated by examination of the infrared spectrum. By this unequivocal method of diagnosis, diosterol-I and diosterol-II were both found to contain one α,β -unsaturated ketonic group and one hydroxyl group; the latter group disappears on benzoylation. On the basis of the combined evidence we now propose the formulas V, VII, and VIII for diosterol-II, diosterol-I, and the enol acetate. The ultraviolet maxima calculated for structures VII and VIII are in good agreement with the values found.³ The intense band at 265 $m\mu$ found for diosterol-II corresponds to that calculated for structure V; the second intense band at 300 $m\mu$ may be indicative of another form. The possibility that the substance suffers isomerization to diosterol-I on irradiation in alcoholic solution was eliminated by a test experiment. Since the maximum is close to that expected for the trienediol VI, it is possible that this substance is present in solution in equilibrium with V; the diol may be an intermediate in the acid isomerization of diosterol-II into diosterol-I.

The new formulas suggested account adequately for the formation and reactions of the compounds. The production of the enol acetate (VIII) by the action of potassium acetate on the unsaturated dibromoketone XV in alcoholic solution must proceed by a special mechanism to account for acetylation under nonacetylating conditions, and we suggest the path of allylic shift of bromine (XIV), replacement of the bromine atoms by acetoxyl groups (XIII), and acetyl migration from C₄ to C₃ through the cyclic acetal XI (see analogy below). That diosterol-II on oxidation with hydrogen peroxide yields the Diels acid (7), whereas diosterol-I yields 7-keto-Diels acid (5) is explained by the presence in diosterol-I of a double bond extending to position 7; a likely hypothesis is that hydrogen peroxide adds 1,4 to the $\Delta^4,6$ -diene system to give the intermediate X.

Petrow and Starling (7) found a new method for the preparation of diosterol-I consisting in mild oxidation of the 3-monoacetate of Δ^5 -cholestene-3,4-diol



³ The chromophore of longer-wavelength absorption in VIII is the Δ^6 -4-ketonic system; that in V is the Δ^2 -4-ketonic system carrying the strongly bathochromic enolic hydroxyl group.



(XVI) to a ketoxide, which was then hydrolyzed. We suggest the structure XVII for the ketoxide (the orientation shown for the oxide ring is arbitrary), and interpret its formation as proceeding through a known migration of the acetyl group from the 3- to the 4-position in acetic acid solution (10, 11).

EXPERIMENTAL PART

The enol acetate VIII (m.p. 159°) and diosterol-I (m.p. 160–161°) were prepared according to Inhoffen (4). Diosterol-II (m.p. 134°) was obtained according to Petrow and Starling (7), but the yield was low and the process uncertain.

Diosterol-I benzoate. A mixture of diosterol-I (200 mg.), benzoyl chloride (2 cc.) and pyridine (2 cc.) was warmed on the steam-bath for one hour, poured into water, and the mixture extracted with ether. The ethereal solution was washed free of pyridine and of acid and the neutral product collected and crystallized from alcohol. The substance formed colorless needles, m.p. 160°.

Anal. Calc'd for $C_{31}H_{48}O_2$: C, 81.27; H, 9.16.

Found: C, 81.27; H, 9.26.

Diosterol-I monosemicarbazone was obtained by heating diosterol-I with semicarbazide hydrochloride in pyridine for one hour on the steam-bath. The derivative separated from alcohol as a faintly yellow crystalline powder, m.p. 252–253°, decomp.

Anal. Calc'd for $C_{31}H_{46}N_2O_2$: N, 9.23. Found: N, 9.52.

This result corresponds with that of Petrow and Starling (7), who obtained a monodinitrophenylhydrazone; Inhoffen (4) reports the preparation of a dioxime.

Diosterol-II benzoate. A mixture of 4,6-dibromocholestenone (400 mg.), sodium benzoate (1 g.) and alcohol (40 cc.) was refluxed for three hours, diluted to turbidity with water, and cooled. The solid that separated was washed with dilute ammonia, water, and alcohol and the benzoate (200 mg.) crystallized from alcohol. It forms colorless needles, m.p. 176–177°.

Anal. Calc'd for $C_{31}H_{46}O_2$: C, 81.27; H, 9.16.

Found: C, 81.36; H, 9.39.

Absorption spectra. Measurements in the ultraviolet (absolute ethanol) were made with a Beckman spectrophotometer, those in the infrared (2.5% solutions in carbon tetrachloride) with the Baird instrument Model B No. 115 (12). The positions of the infrared bands associated with the vibrations of the α,β -unsaturated carbonyl and ester groups correspond, with allowance for vicinal effects, to bands found for comparable steroids.⁴

The ultraviolet absorption maximum calculated for diosterol-I benzoate is 290 $m\mu$, which agrees with the position of the more intense of the two bands found. The second band at 232 $m\mu$ must be associated with the benzoyl group; in the case of diosterol-II benzoate the sole band found was in this region.

SUMMARY

A method for calculation of ultraviolet absorption maxima is presented that is applicable to both heteroannular and homoannular dienes and polyenes, and to substituted or unsubstituted enones and polyenones.

⁴ Data kindly communicated by Drs. R. N. Jones and K. Dobriner (publications in press).

Evidence of ultraviolet and infrared spectroscopy shows that the structures previously assigned to the diosterols and their derivatives are in error. New structures are proposed that account for all of the facts.

CAMBRIDGE, MASS.

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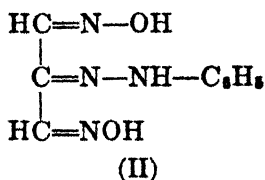
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2-PHENYL-2,1,3-TRIAZOLE-4-CARBOXALDEHYDE
AND DERIVATIVES¹

J. L. RIEBSOMER AND GENE SUMRELL

Received May 3, 1948²

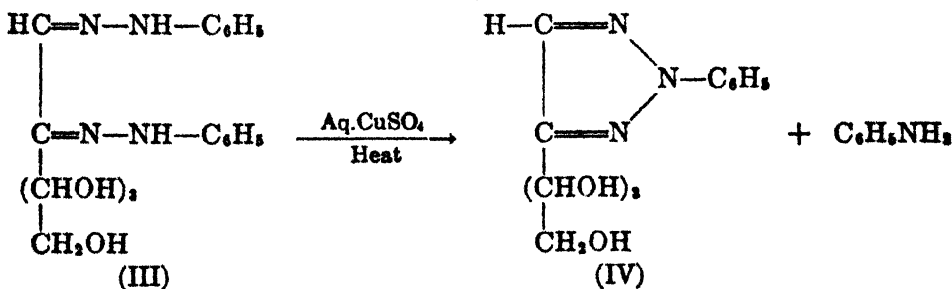
2-Phenyl-2,1,3-triazole-4-carboxaldehyde (I) was first synthesized by von Pechmann (1) who treated the hydrazoxime (II)



with phosphorus pentachloride, or boiled it with acetic anhydride. These methods produced the oxime of (I) in 20 to 25% yields. An alternative procedure was to heat the monoacetate of (II) with dilute sodium carbonate which produced a 50% yield of the oxime of (I).

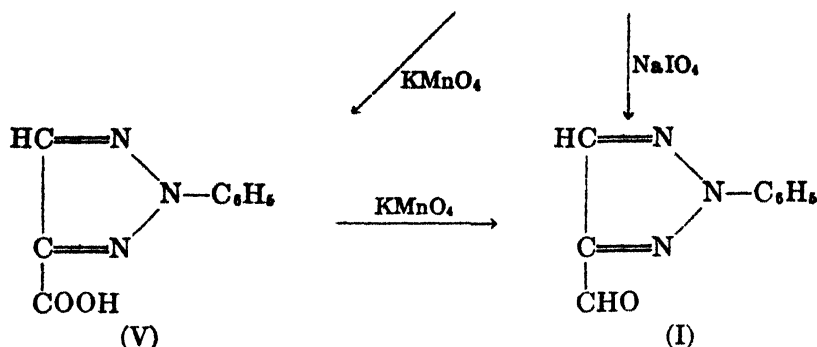
A much more satisfactory method was discovered in 1944 by Hann and Hudson (2), who isolated (I) in connection with the proof of structure of "phenyl-D-glucosotriazole" (IV), a product of the action of copper sulfate on phenyl-D-glucosazone (III). The osotriazole showed good crystallizing power and a sharp melting point and was superior to the osazone for the characterization of glucose. Upon oxidation with sodium periodate it gave 2-phenyl-2,1,3-triazole-4-carboxaldehyde (I) in high yield and the latter compound was further identified by oxidation with permanganate to 2-phenyl-2,1,3-triazole-4-carboxylic acid (V).

Hann and Hudson were interested in the osotriazole aldehyde only as an adjunct to the proof of structure of the sugar osotriazoles, of which they subsequently prepared a large number. However, since the aldehyde was not readily available from von Pechmann's method, the relatively direct method of Hann and Hudson seemed to open an avenue by which the chemistry of (I) and (V) might be extended without too much difficulty.



¹ A portion of this publication was abstracted from the thesis presented by Mr. Sumrell to the graduate faculty of the University of New Mexico, in partial fulfillment of the requirements for the M. S. degree.

² Revised manuscript, with additional experimental results received July 13, 1948.

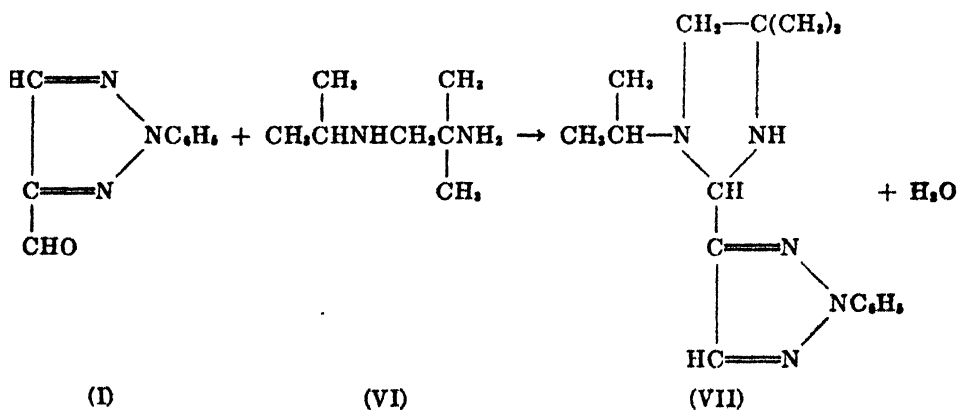


In the present work it has been shown that the above procedure can be adapted readily to larger scale production of (I) and (V) and that the over-all yield of (I) may be as high as 60%.

The aldehyde (I) was converted readily to some of the common aldehyde derivatives such as its semicarbazone and 2,4-dinitrophenylhydrazone. It reacted with acetophenone to form 2-phenyl-2,1,3-triazole-4-carboxalacetophenone, and with acetone to give bis-(2-phenyl-2,1,3-triazol-4-ylmethylene)-acetone. It is probable that (I) will condense similarly with all methyl ketones.

When the aldehyde (I) was subjected to the usual conditions for the Perkin synthesis a good yield of 2-phenyl-2,1,3-triazol-4-ylmethylene acetic acid was obtained. von Pechmann (3) showed that (I) underwent the Cannizzaro reaction. This work has been corroborated.

Imidazolidines can be prepared from (I) by heating it at relatively low temperatures with 1,2-diamines under conditions to remove water. In a typical example (I) was heated in equimolecular quantity with N-(2-aminoisobutyl)isopropylamine (VI) to produce 1-isopropyl-2-(2'-phenyl-2',1',3'-triazol-4'-yl)-4,4-dimethylimidazolidine (VII).

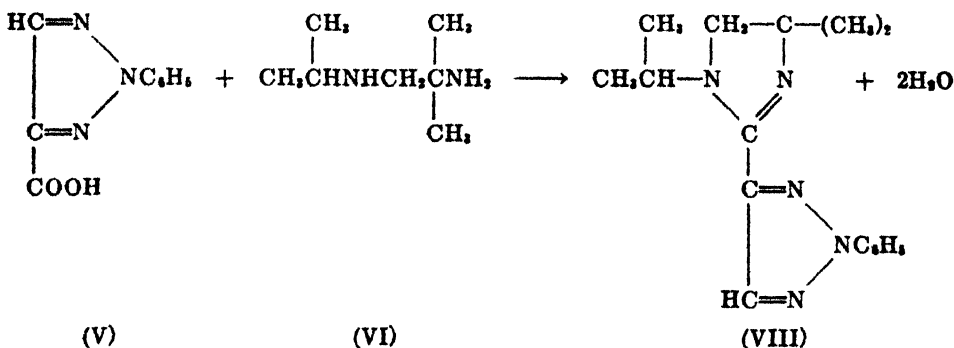


The aldehyde (I) reacted typically with Grignard reagents to form the expected secondary alcohols.

A number of derivatives of (V) have also been prepared. The methyl and ethyl esters and the amide of (V) were prepared previously by von Pechmann.

This work has been repeated. The phenyl and diethylaminoethanol esters have now been produced by conventional methods.

The acid (V) was found to react typically with 1,2-diamines to produce the expected imidazolines. Thus when (V) was heated with (VI) under conditions to remove water, a 93% yield of 1-isopropyl-2-(2'-phenyl-2',1',3'-triazol-4'-yl)-4,4-dimethyl-2-imidazoline (VIII) was obtained.



Thus it is observed that the aldehyde (I) behaves generally like benzaldehyde. One interesting difference has been observed. (I) is soluble in alkali but is not sufficiently acidic to be titrated with a dilute base. Triazoles not possessing an N-substituent are decidedly acidic in character. However, 2-phenyl-2,1,3-triazole is insoluble even in concentrated alkali. Therefore, it would appear that the hydrogen atom attached to the carbonyl carbon of (I) is labile. This would be expected from electronic considerations. The triazole ring is a resonating structure and probably is even more electron attracting than the phenyl group. Consequently, it would be expected that the electrons would tend to be drawn away from the carbonyl carbon and toward the triazole ring and hence the hydrogen atom attached to the carbonyl carbon would be somewhat active.

EXPERIMENTAL

Preparation of 2-phenyl-2,1,3-triazole-4-carboxaldehyde (I). The osazone of glucose was prepared in substantially quantitative yields by standard methods, starting with sucrose and phenylhydrazine hydrochloride. In a typical experiment for the preparation of phenyl-D-glucosotriazole (IV), 260 g. of phenyl-D-glucosazone was suspended in a solution containing 364 g. of cupric sulfate pentahydrate in 15 l. of water. After refluxing 2 hours, the yellow osazone had completely disappeared, and the mixture was dark in color. It was observed that prolonged heating should be avoided, since it resulted in a greater amount of tar formation.

After the reaction was completed, decolorizing charcoal was added, and the hot solution filtered as fast as possible. Upon standing, crystallization took place in the filtrate. More product was obtained by evaporating the filtrate to about one-fifth its original volume. It was necessary to crystallize a second time to obtain a colorless product, with the melting point 195–196°; yield 112 g. (59%).

The conversion of "phenyl-D-glucosotriazole" (IV) to the aldehyde (I) was made by dissolving 607 g. of sodium periodate in 12 l. of water and adding 225 g. of (IV). The mixture was stirred 24 hours at room temperature, and the solid aldehyde was filtered and dried; yield almost quantitative.

Conversion of (I) to 2-phenyl-2,1,3-triazole-4-carboxylic acid (V). To a solution containing 10 g. of potassium hydroxide in 400 ml. of water was added 34.6 g. (0.1 mole) of (I), and while heating over steam and stirring, 41 g. of potassium permanganate was added in small portions. Sodium bisulfite was added to destroy the excess permanganate, the brown manganese dioxide was filtered, and the filtrate acidified with hydrochloric acid. A white precipitate formed which was filtered and dried; yield 33.2 g. (87%), melting point 190–192°. A small portion was recrystallized from water for analysis.

Anal. Calc'd for $C_9H_7N_3O_2$: C, 57.17; H, 3.73; N, 22.16.

Found: C, 57.55; H, 3.52; N, 22.50.

Conversion of "phenyl-D-glucosotriazole" (IV) to 2-phenyl-2,1,3-triazole-4-carboxylic acid (V). When it became apparent that considerable quantities of (V) would be needed, it was found that it could be prepared directly by permanganate oxidation of (IV), thus eliminating the sodium periodate step. To a mixture of 400 ml. of water, 8 g. of potassium hydroxide, and 23 g. of (IV), was added portionwise 80 g. of potassium permanganate while stirring and warming over steam. Sodium bisulfite was added to destroy the excess of permanganate. The brown manganese dioxide was filtered and the filtrate acidified with hydrochloric acid. A white precipitate of (V) formed, yield 13.3 g. (82%), melting point 191–192°.

Preparation of the 2,4-dinitrophenylhydrazones of (I). A solution was prepared containing 1.73 g. (0.01 mole) of (I) and 1.98 g. (0.01 mole) of 2,4-dinitrophenylhydrazine in 100 ml. 95% ethanol. It was heated to boiling and 20 ml. of concentrated hydrochloric acid was added. A precipitate formed immediately, and the mixture was refluxed 5 minutes. The crystals which formed melted at 198–200°. Crystallization from a chloroform-ethanol mixture did not change the melting point; yield 3.5 g. (almost quantitative).

Anal. Calc'd for $C_{11}H_{11}N_7O_4$: N, 27.74. Found: N, 28.21.

Preparation of the semicarbazone of (I). A solution was prepared containing 2 g. of (I) in 25 ml. of ethanol. Another solution contained 2 g. of semicarbazide hydrochloride and 3 g. of sodium acetate in 20 ml. of water. The two solutions were mixed and warmed over steam 30 minutes. A white solid formed melting at 225–226°, yield 2.6 g. (almost quantitative).

Anal. Calc'd for $C_{10}H_{10}N_4O$: N, 36.52. Found: N, 37.02.

Preparation of 2-phenyl-2,1,3-triazol-4-yl carbinol, by a crossed Cannizzaro reaction. To a suspension of 26 g. (0.15 mole) of (I) in 42.2 ml. (0.60 mole) of 38% formaldehyde was added 18 g. (0.45 mole) of sodium hydroxide in 36 ml. of water. The mixture was agitated occasionally, and sufficient heat was generated by the reaction so that external warming was unnecessary. After the mixture had cooled, it was acidified with hydrochloric acid and then neutralized with sodium carbonate. After cooling, the alcohol was filtered and recrystallized from water containing a little alcohol. The yield was 14.5 g. (55%) and the product melted at 64–65°, which corresponds with the melting point previously reported.

Anal. Calc'd for $C_9H_9N_3O$: N, 23.99. Found: N, 23.90.

Acidification of the sodium carbonate filtrate produced 2.5 g. of 2-phenyl-2,1,3-triazole-4-carboxylic acid, melting point 191–192°. The combined yields of the two products account for 63% of (I).

Reaction of (I) with acetophenone. A solution was prepared containing 1.73 g. (0.01 mole) of (I), 1.2 g. (0.01 mole) of acetophenone in 35 ml. of ethanol. This solution was cooled in an ice-bath and to it was added dropwise with stirring a solution containing 0.5 g. of potassium hydroxide in 5 ml. of water. This mixture was allowed to stand 1.5 hours in the ice-bath. A solid formed which weighed 2.4 g. (87%) and melted at 131–132°. A portion was recrystallized for analysis without raising the melting point.

Anal. Calc'd for $C_{17}H_{15}N_3O$: C, 74.24; H, 4.03; N, 15.28.

Found: C, 74.01; H, 4.52; N, 15.41.

Synthesis of bis-(2-phenyl-2,1,3-triazol-4-ylmethylene)acetone (IX). A solution of 8.7 g. (0.05 mole) of (I) in 135 ml. of ethanol and 1.75 ml. (0.025 mole) of acetone was cooled in an ice-bath and to it was added dropwise a solution of 2.5 g. of potassium hydroxide in

25 ml. of water. The mixture was kept at 0° for 2 hours, and one hour at room temperature. A yellow precipitate formed which was crystallized from a benzene-alcohol mixture. The yield was 4.3 g. (47%) and the product melted at 194–195°.

Anal. Calc'd for $C_{21}H_{16}N_6O$: N, 22.82. Found: N, 23.02.

Preparation of 2-phenyl-2,1,3-triazol-4-ylmethyleneacetic acid. A mixture of 8.5 g. of (I), 2.5 g. of anhydrous sodium acetate, and 7.5 g. of acetic anhydride was heated at 180° for 8 hours. The product was poured into sodium carbonate solution and the insoluble material removed by filtration. The filtrate was acidified with hydrochloric acid, giving a white precipitate which melted at 175–180°; yield 9.4 g. of the crude product (88%). It was recrystallized from hot water. The purified product melted at 179–181°; yield of pure product 6.5 g. (61%).

Anal. Calc'd for $C_{11}H_8N_4O_2$: N, 19.53; Neutr. Equiv., 215.06.

Found: N, 20.33; Neutr. Equiv., 213.6.

Preparation of ethyl-2-phenyl-2,1,3-triazol-4-ylmethylene acetate. A mixture of 50 ml. of absolute ethanol, 13.2 g. of 2-phenyl-2,1,3-triazol-4-ylmethylene acetic acid, and 2 ml. of concentrated sulfuric acid was refluxed ten hours. The excess ethanol was removed *in vacuo* and the residue washed with 5% aqueous sodium carbonate. The ester was dissolved in ether and dried over sodium sulfate. The ether solution was decanted, the ether removed *in vacuo*, and the residue crystallized from methanol; yield 6.7 g., m.p. 64–66°.

Anal. Calc'd for $C_{13}H_{12}N_4O_2$: N, 17.28. Found: N, 17.55.

Attempted synthesis of 2-phenyl-2,1,3-triazol-4-yl-hydroxyacetic acid. A mixture of 17.3 g. (0.10 mole) of (I), 6.5 g. (0.1 mole) of potassium cyanide, and 20 ml. water was treated slowly with stirring and cooling with 30 ml. of sodium bisulfite. During the reaction a semisolid formed and the mixture darkened considerably. This semisolid layer (presumably the cyanohydrin) was refluxed with concentrated hydrochloric acid. The product remaining was a yellow-brown sticky solid from which nothing could be crystallized.

Preparation of 1-isopropyl-2-(2'-phenyl-2',1',3'-triazol-4'-yl)-4,4-dimethylimidazolidine (VII). A mixture of 8.7 g. (0.05 mole) of (I), 6.5 g. (0.05 mole) of N-(2-aminoisobutyl)-isopropylamine, and about 100 ml. of benzene was heated under conditions such that a benzene-water mixture was distilled through a four-foot packed column. The column was fitted with a head so that the benzene was returned and the water separated. The temperature was gradually increased to 100°, resulting in the removal of 0.8 g. of water. An increase of the temperature to 120° caused no more water to separate. The excess of benzene was removed *in vacuo*. Ethanol was added to the residue, and upon cooling, one gram of a white solid (m.p. 197–198°) crystallized. The filtrate from this crystallization was distilled. The entire residue (after a small forerun) boiled at 181–182° at 3 mm.; yield 9.0 g. (63%).

Anal. Calc'd for $C_{18}H_{22}N_6$: N, 24.56. Found: N, 24.22.

Preparation of 1-n-butyl-2-(2'-phenyl-2',1',3'-triazol-4'-yl)-4,4-dimethylimidazolidine (X). A mixture of 8.7 g. (0.05 mole) of (I), 7.2 g. of N-(2-aminoisobutyl) n-butylamine, and about 100 ml. of benzene was heated as in the preceding experiment. About 0.8 g. of water was removed. The benzene was removed *in vacuo*, and ethanol was added to the residue. All but about one gram of solid dissolved. This solid was filtered and the filtrate distilled. After the ethanol and a few drops of forerun were removed, the entire product boiled at 196–198° at 4 mm.; yield 11 g. (73%). It was light yellow in color and was redistilled. A middle fraction of 7 g. was taken which was light yellow in color and boiled at 184° at 1 mm.

Anal. Calc'd for $C_{27}H_{32}N_6$: N, 23.39. Found: N, 23.32.

Preparation of 1-phenyl-2-(2'-phenyl-2',1',3'-triazol-4'-yl)-4,4-dimethylimidazolidine (XI). A mixture of 8.7 g. (0.05 mole) of (I) and 8.2 g. (0.05 mole) of N-(2-aminoisobutyl)-aniline, and about 100 ml. of benzene was heated under the same conditions as in the preceding experiment. About 0.8 g. of water was removed. The product upon distillation boiled at 230–235° at 2 mm.; yield 10 g. (62%). The distillation was difficult and some decomposition took place. The distillate partially solidified upon standing, and, was

crystallized from ethanol. About 1 g. of solid formed. The filtrate was redistilled and a 5.3-g. middle cut was taken for analysis and testing. It was a thick syrup.

Anal. Calc'd for $C_{15}H_{21}N_3$: N, 21.93. Found: N, 21.44.

Preparation of 1-p-tolyl-2-(2'-phenyl-2',1',3'-triazol-4'-yl)-4,4-dimethylimidazolidine (XII). A mixture of 8.7 g. (0.05 mole) of (I), 8.9 g. (0.05 mole) of N-(2-aminoisobutyl)-p-toluidine, and about 100 ml. of benzene was heated one hour at 105° as in the preceding experiment to remove water. The benzene was removed *in vacuo* and the residue was purified by crystallization from an alcohol-water mixture. The yield was 6.1 g. (51%) and the product melted at 109–110°.

Anal. Calc'd for $C_{25}H_{31}N_5$: N, 21.09. Found: N, 21.14.

Synthesis of methyl-2-phenyl-2,1,3-triazol-4-yl carbinol. A Grignard reagent was prepared in the usual manner using 16.2 g. (0.17 mole) of methyl iodide and 3.9 g. (0.16 mole) of magnesium. To this Grignard reagent was added 8.5 g. (0.05 mole) of (I) dissolved in 60 ml. of anhydrous ether. The mixture was refluxed 30 minutes, cooled, and poured into ice-water containing 10% sulfuric acid. The ether layer was separated, dried over sodium sulfate, and distilled at 3 mm. The product boiled at 144°; yield 5.5 g. (59%).

Anal. Calc'd for $C_{10}H_{11}N_3O$: N, 22.21. Found: N, 21.86.

Synthesis of ethyl-2-phenyl-2,1,3-triazol-4-yl carbinol. A Grignard reagent was prepared from 13.1 ml. (0.17 mole) of ethyl bromide and 3.9 g. (0.16 mole) of magnesium under the usual conditions. To this Grignard reagent was added 8.5 g. (0.05 mole) of (I) dissolved in 60 ml. of dry ether. After the addition, the mixture was refluxed 30 minutes. It was poured into ice-water containing sulfuric acid, the ether layer was separated, dried over sodium sulfate and distilled. The product boiled at 156° at 3 mm., yield 4.7 g. (47%).

Anal. Calc'd for $C_{11}H_{13}N_3O$: N, 20.68. Found: N, 20.30.

Synthesis of phenyl-2-phenyl-2,1,3-triazol-4-yl carbinol. A Grignard reagent was prepared in the usual manner from bromobenzene (0.17 mole) and magnesium (0.16 mole). To this reagent were added 8.7 g. (0.05 mole) of (I) dissolved in 60 ml. of dry ether. After the addition was complete, the mixture was refluxed 30 minutes and then introduced into ice-water containing sulfuric acid. The ether layer was separated, dried over sodium sulfate, and distilled at 3 mm. It boiled at 214°; yield 7.2 g. (58%).

Anal. Calc'd for $C_{18}H_{15}N_3O$: N, 16.72. Found: N, 17.14.

Conversion of (V) to its acid chloride (XIII). A mixture of 1.89 g. (0.01 mole) of 2-phenyl-2,1,3-triazole-4-carboxylic acid and 2 g. (0.01 mole) of phosphorus pentachloride was warmed gently to start the reaction. The mixture became quite hot and changed to a molten mass, which solidified upon cooling. The product was warmed over steam *in vacuo* to remove the phosphorus oxychloride. A white solid remained which was used for other reactions without purification. In another experiment thionyl chloride was substituted for the phosphorus pentachloride but the results were less satisfactory.

Synthesis of methyl 2-phenyl-2,1,3-triazole-4-carboxylate. About 5 ml. of absolute methanol was added to 0.01 mole of the acid chloride (XIII) prepared in the preceding experiment. The mixture was warmed gently. After a few minutes a white solid began to crystallize, melting point 85–86°. A second crystallization did not raise the melting point; yield 1.6 g. (79%).

Anal. Calc'd for $C_{10}H_9N_3O_2$: C, 59.14; H, 4.47; N, 20.68.

Found: C, 58.90; H, 4.02; N, 20.95.

Synthesis of phenyl-2-phenyl-2,1,3-triazole-4-carboxylate. To 6.2 g. (0.03 mole) of the acid chloride (XIII) was added 3.8 g. of phenol and 15 ml. of pyridine. This mixture was allowed to stand 4 hours and was then refluxed 3 hours. Upon pouring into ice-water a semi-solid appeared. The water was decanted and the semisolid washed with water containing 3% sodium carbonate. The insoluble residue was dissolved in ethanol from which it crystallized; yield 3 g. (50%), melting point 111–112°.

Anal. Calc'd for $C_{18}H_{15}N_3O_2$: N, 15.81. Found: N, 15.92.

Synthesis of the amide of 2-phenyl-2,1,3-triazole-4-carboxylic acid. To 0.01 mole of the acid chloride (XIII) was added 5 ml. of concentrated ammonium hydroxide. The mixture

was stirred and warmed gently for 15 minutes. A white solid formed which when crystallized from 95% ethanol melted at 142–143°; yield quantitative.

Anal. Calc'd for $C_8H_8N_4O$: N, 29.77. Found: N, 29.90.

Preparation of the anilide of 2-phenyl-2,1,3-triazole-4-carboxylic acid. To 0.01 mole of the acid chloride (XIII) was added 1.86 g. (0.02 mole) of aniline dissolved in anhydrous ether. A heavy white precipitate formed at once. The mixture was stirred and warmed gently 15 minutes. The ether was removed and water added to dissolve the aniline hydrochloride. The solid was filtered and crystallized from 95% ethanol; yield 1.9 g. (73%), melting point 154–155°. A second crystallization did not raise the melting point.

Anal. Calc'd for $C_{15}H_{13}N_4O$: N, 21.20. Found: N, 21.72.

Synthesis of the hydrochloride of the diethylaminoethanol ester of 2-phenyl-2,1,3-triazole-4-carboxylic acid. To 14.5 g. (0.07 mole) of the acid chloride (XIII) was added 40 g. of diethylaminoethanol. Much heat was evolved. After the reaction subsided, the mixture was warmed over steam 2 hours, and added to about 1 liter of 2% sodium carbonate solution. An oil came to the top which was extracted with ether, washed with water, and dried over sodium sulfate. The ether solution was decanted and treated with anhydrous hydrogen chloride. The slightly colored hydrochloride formed, upon crystallizing twice from ethanol was colorless, and melted at 189–190°; yield 11.8 g. (51%).

Anal. Calc'd for $C_{15}H_{21}ClN_4O_2$: N, 17.25; Cl, 10.96.

Found: N, 17.17; Cl, 10.92.

Nitration of 2-phenyl-2,1,3-triazole-4-carboxylic acid. A mixture of 4.2 g. of the acid (V) and 6.6 ml. of concentrated sulfuric acid was cooled in an ice-salt bath and 3.3 ml. of concentrated nitric acid was added dropwise with stirring. After the addition was complete the mixture was allowed to stand at room temperature 30 minutes and then poured into 50 ml. of cold water. The solid which formed was crystallized from 95% ethanol; yield 3.1 g. (60%), melting point 236–238°.

Anal. Calc'd for $C_9H_6N_4O_4$: N, 23.92. Found: N, 24.16.

The position of the nitro group has not been proved, but it is reasonable to expect it to appear in the 4-position.

Synthesis of 1-isopropyl-2-(2'-phenyl-2',1',3'-triazol-4'-yl)-4,4-dimethyl-2-imidazoline (VII). A mixture of 17 g. of 2-phenyl-2,1,3-triazole-4-carboxylic acid, 11.7 g. of N-(2-aminoisobutyl)isopropylamine, and about 100 ml. of benzene was heated under the usual conditions to remove the water formed from the reaction as an azeotropic mixture. No water was driven over until the temperature reached about 200°. From 200–230° 1.4 g. of water came over. After cooling, the product was washed with 200 ml. of 5% sodium hydroxide. The oil remained undissolved, was extracted once with benzene and once with ether. The combined extracts were dried over solid potassium hydroxide, and distilled. After a small forerun the entire product boiled at 190° at 4 mm., yield 11.7 g. (93%). This yield is based upon the fact that 3 g. of the acid was recovered from the sodium hydroxide washing.

Anal. Calc'd for $C_{18}H_{21}N_5$: N, 24.72. Found: N, 24.82.

Synthesis of 1-n-butyl-2-(2'-phenyl-2',1',3'-triazol-4'-yl)-4,4-dimethyl-2-imidazoline (XIV). A mixture of 18.9 g. (0.1 mole) of (V), 14.4 g. (0.1 mole) of N-(2-aminoisobutyl)n-butylamine, and 100 ml. of benzene was heated at 245° for one hour under the usual conditions to remove water. The product was washed with 5% sodium hydroxide and the oil which remained was extracted once with benzene and once with ether. The combined ether and benzene extracts were dried over solid potassium hydroxide and distilled. The main product boiled at 196° at 4 mm. The yield of XIV was 18.8 g. (77%). This calculation of the percentage yield considered the fact that 3.2 g. of (V) was recovered by acidifying the alkaline extract.

Anal. Calc'd for $C_{17}H_{24}N_4$: N, 23.52. Found: N, 23.26.

The picrate of (XIV) was prepared by refluxing a solution of 1.9 g. of (XIV) and 1.6 g. of picric acid in 10 ml. of ethanol for 15 minutes. A yellow solid formed upon cooling, which upon purification by crystallization from ethanol melted at 141–143°.

Anal. Calc'd for $C_{15}H_{13}N_3O_2$: N, 21.28. Found: N, 21.41.

The hydrochloride of XIV was prepared by dissolving 2 g. in dry ether and adding excess dry hydrogen chloride. The white solid hydrochloride was filtered and purified by crystallization from a benzene-acetone mixture. It melted at 220–222°.

Anal. Calc'd for $C_{15}H_{13}ClN_3$: N, 20.98. Found: N, 20.78.

PHARMACOLOGICAL STUDIES

The semicarbazone of 2-phenyl-2,1,3-triazole-4-carboxaldehyde, 2-phenyl-2,1,3-triazole-4-carboxylic acid, and 2-phenyl-2,1,3-triazol-4-ylmethyleneacetic acid proved to be ineffective in the treatment of tetanus toxemia, *Streptococcus hemolyticus*, influenza virus, and rabic virus infected mice. The latter compound had no bactericidal, bacteriostatic, fungicidal, or fungistatic action toward common organisms.

The hydrochloride of the diethylaminoethyl ester of 2-phenyl-2,1,3-triazole-4-carboxylic acid was ineffective as an antispasmodic and had little antihistamine activity. Likewise it was ineffective as a local anesthetic.

1-Isopropyl-2-(2'-phenyl-2',1',3'-triazol-4'-yl)-4,4-dimethyl-2-imidazoline proved ineffective against tuberculosis. The same can be said for 1-isopropyl-2-(2'-phenyl-2',1',3'-triazole-4'-yl)-4,4-dimethylimidazolidine and 1-*n*-butyl-2-(2'-phenyl-2',1',3'-triazol-4'-yl)-4,4-dimethylimidazolidine.

1-Phenyl-2-(2'-phenyl-2',1',3'-triazol-4'-yl)-4,4-dimethylimidazolidine was not effective against tuberculosis or as an antimalarial. No appreciable bactericidal, bacteriostatic, fungicidal, or fungistatic action was observed for any of the other imidazolines or imidazolidines reported above.

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SUMMARY

1. Twenty-seven derivatives of 2-phenyl-2,1,3-triazole-4-carboxaldehyde have been prepared.

2. Some of these compounds have been examined for therapeutic value but none has proved to be effective.

ALBUQUERQUE, NEW MEXICO

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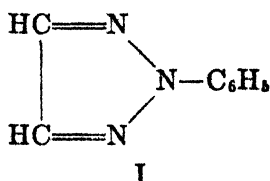
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2-PHENYL-2,1,3-TRIAZOLE AND DERIVATIVES

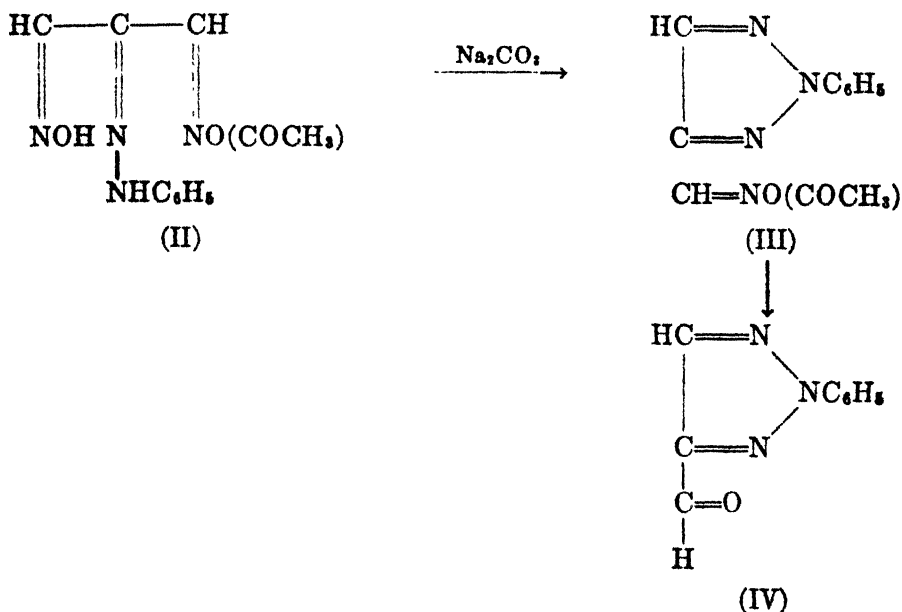
J. L. RIEBSOMER

Received May 3, 1948

The synthesis of 2-phenyl-2,1,3-triazole (I) was reported by von Pechmann



(1) who decarboxylated the silver salt of 2-phenyl-2,1,3-triazole-4-carboxylic acid by heating the latter compound in a retort. The 2-phenyl-2,1,3-triazole-4-carboxylic acid was obtained by heating (II) with 10% aqueous sodium carbonate.



This treatment first resulted in ring closure, forming the acetylated oxime (III), which in turn was hydrolyzed to 2-phenyl-2,1,3-triazole-4-carboxaldehyde (IV). The aldehyde was oxidized readily to the corresponding acid (2).

The yield of (I) was quite low, following the above series of reactions. It has been demonstrated that (I) can be prepared with an over-all yield of about 60% by heating the osazone of glyoxal with aqueous cupric sulfate. This method is an adaptation of that used by Hann and Hudson (3) for the synthesis of substituted osotriazoles from the sugar osazones. Because of the simpler structure of

glyoxal osazone, the 2-phenyl-2,1,3-triazole is obtained directly from its phenyl-osazone through decomposition with aqueous copper sulfate. The synthesis of (I) is simpler because it does not involve the side chain oxidation with sodium periodate as in the aldehyde preparation.

von Pechmann (1) produced a mononitro derivative (m.p. 183–184°) of (I) by treating it with fuming nitric acid. He gave no indication regarding the orientation of the nitro group. Upon nitration of (I) with a cold sulfuric-nitric acid mixture we obtained two mononitro derivatives. One of these compounds melted at 183–184° and was formed in high yield. The second melted at 126–127° and was obtained in low yield. On the basis of the general rules of orientation one would expect the *p*-isomer to melt higher and to be produced in greater quantity. Therefore, it is believed that the compound which melted at 183–184° is the *p*-isomer and the one which melted at 126–127° is the *o*-isomer. An effort was made to prove unequivocally the structure of the *p*-isomer by subjecting the *p*-nitrophenyl osazone of glyoxal to conditions which might effect a ring closure to form 2-(4'-nitrophenyl)-2,1,3-triazole (V) directly. All attempts to do so resulted in failure. When the *p*-nitrophenylosazone was heated with aqueous cupric sulfate no change was observed even in a sealed tube at 200°. The presence of the nitro group either reduces the reactivity of the osazone, or its inability to react may result from its extremely low solubility in water. When the osazone was heated with acetic anhydride, ring closure also failed.

Proceeding on the assumption that reduced solubility might have caused the failure of the ring closure, the *p*-nitrophenylosazone of glucose was prepared. Because of the hydroxylated side chain this osazone should be more soluble in water than the osazone of glyoxal. The *p*-nitrophenylosazone of glucose was heated with aqueous cupric sulfate but the expected ring closure again failed. Accordingly it is believed that the presence of the nitro group in these osazones markedly reduces their reactivity.

While compounds (I) and (V) have been prepared previously, there was no literature reference found describing any derivatives of (V). Several such derivatives have now been prepared and some of them have been examined for possible medicinal uses.

When (V) was reduced with tin and hydrochloric acid, 2-(4'-aminophenyl)-2,1,3-triazole (VI) was produced in good yield. The hydrochloride, acetyl, and benzoyl derivatives of (VI) were prepared by the usual methods.

When compound (V) was subjected to the usual conditions for the diazotization of an aromatic amine, some diazotization took place, but for some unexplained reason the yields were not very satisfactory. The diazonium salt coupled with beta-naphthol to give a red solid which analyzed correctly for the expected 1-*p*-[2'-(2',1',3'-triazolybenzene-azo)]-2-naphthol. When the diazonium salt was treated under the usual conditions of the Bart reaction, 2-(4'-arsonophenyl)-2,1,3-triazole was produced with an over-all yield of 27%. But when the diazonium salt solution was warmed none of the expected 2-(4'-hydroxyphenyl)-2,1,3-triazole was obtained.

When the amino compound (VI) was allowed to react with *p*-acetylamino-

benzenesulfonyl chloride, a good yield of the acetyl derivative of 2-(*p*-sulfanilamido)phenyl-2,1,3-triazole was obtained, which upon hydrolysis gave 2-(*p*-sulfanilamido)phenyl-2,1,3-triazole.

2-Phenyl-2,1,3-triazole was treated with chlorosulfonic acid. The product formed was not purified but was assumed to be *p*-2-(2,1,3-triazolyl)benzenesulfonyl chloride. When ammonium hydroxide was added to a portion of this sulfonyl chloride a white solid formed which analyzed correctly for *p*-2-(2,1,3-triazolyl)benzenesulfonamide. Following the usual procedure the sulfonyl chloride was treated with aniline to produce *p*-2-(2,1,3-triazolyl)benzenesulfonanilide.

2-Phenyl-2,1,3-triazole was mixed with acetyl chloride and aluminum chloride hoping to bring about a typical Friedel-Crafts reaction, but under the conditions tried none of the expected reaction took place.

EXPERIMENTAL

Synthesis of 2-phenyl-2,1,3-triazole (I). In a typical experiment a solution was prepared containing 115.6 g. (0.8 mole) of phenylhydrazine hydrochloride, 218 g. of sodium acetate, and 1 liter of water. While stirring this solution at room temperature, 74 g. of 30% glyoxal (0.4 mole) was added portionwise. More water was added as the reaction proceeded so that the mixture could be stirred. After stirring 4 hours, the yellow osazone of glyoxal was filtered. The yield was practically quantitative (95 g.).

The entire yield of the osazone from above was transferred to a 5-liter flask containing 1 liter of water and 250 g. of cupric-sulfate pentahydrate. This mixture was heated with stirring at 75–80° for 6.5 hours, after which the reaction product was steam distilled to remove the triazole. The triazole-water mixture was saturated with sodium chloride and extracted with ether. The ether extract was washed with 10% hydrochloric acid to remove aniline. It was then washed with water, dried over sodium sulfate, and distilled. A yield of 33 g. (59%) of the triazole was obtained which boiled at 115–118° at 22 mm.

Anal. Calc'd for $C_8H_7N_3$: C, 66.18; H, 4.86; N, 28.94.

Found: C, 66.15; H, 4.72; N, 29.07.

In earlier experiments the triazole was extracted with ether (instead of steam distillation) after heating the osazone with aqueous copper sulfate. The procedure proved to be very unsatisfactory and was discontinued.

Nitration of 2-phenyl-2,1,3-triazole. To 420 ml. of concentrated sulfuric acid was added slowly with cooling 200 g. of 2-phenyl-2,1,3-triazole. Keeping the temperature below 20°, 210 ml. of concentrated nitric acid was added dropwise with stirring. After the nitric acid had been introduced, the mixture was allowed to stand at room temperature one hour and was then poured into 3,000 ml. of cold water. The solid which formed was filtered and dried. This solid was washed thoroughly with ethanol and the washings combined. The solid which remained undissolved melted at 182–184°; yield, 215 g. (82%). A portion was purified for analysis by crystallizing from ethanol.

Anal. Calc'd for $C_8H_6N_4O_2$: N, 29.45. Found: N, 29.53.

The ethanol extract was partially evaporated and, upon cooling, some more of the solid melting at 183° was recovered. The filtrate from this was evaporated and after many crystallizations another solid melting at 126–127° was produced. It is believed to be 2-(2'-nitrophenyl)-2,1,3-triazole.

Anal. Calc'd for $C_8H_6N_4O_2$: N, 29.45. Found: N, 29.53.

Reduction of 2-(4'-nitrophenyl)-2,1,3-triazole to 2-(4'-aminophenyl)-2,1,3-triazole. To 215 g. (1.65 moles) of 2-(4'-nitrophenyl)-2,1,3-triazole was added 344 g. of granulated tin in a 5-liter flask fitted with a condenser. To this mixture was added 1000 ml. of concentrated hydrochloric acid portionwise with gentle heating until the reaction was complete. The mixture was then poured into water. Sodium hydroxide was added in excess and the mixture extracted with benzene. The benzene extract was dried over solid potassium hydroxide and distilled. It boiled at 165° at 2 mm. and solidified upon standing; yield 151.5 g. (84%).

Anal. Calc'd for $C_8H_8N_4$: N, 34.98. Found: N, 34.99.

Conversion of 2-(4'-aminophenyl)-2,1,3-triazole to its hydrochloride. A small sample of the amine was dissolved in anhydrous ether and treated with dry hydrogen chloride. A white precipitate formed at once which was filtered and washed with dry ether. It was then crystallized twice from 98% ethanol.

It melted at 199° with previous softening. The melting point was not sharp.

Anal. Calc'd for $C_8H_8ClN_4$: Cl, 18.03. Found: Cl, 17.97.

Preparation of 2-(4'-acetylaminophenyl)-2,1,3-triazole. To 2 g. of 2-(4'-aminophenyl)-2,1,3-triazole was added 5 g. of acetic anhydride. The mixture was warmed over steam 30 minutes. Water was added and the white solid which formed was filtered, washed with water, and crystallized twice from ethanol; yield 1.5 g., melting point 189–190°.

Anal. Calc'd for $C_{10}H_{10}N_4O$: N, 27.69. Found: N, 27.99.

Preparation of 2-(4'-benzoylaminophenyl)-2,1,3-triazole. To 1 g. of 2-(4'-aminophenyl)-2,1,3-triazole was added 5 ml. of water and 3 g. of benzoyl chloride. To this mixture was added 15 ml. of 20% aqueous sodium hydroxide solution in small portions and with vigorous shaking. A white solid formed which was filtered, washed with water, and crystallized twice from ethanol; yield 1.3 g., melting point 193–194°.

Anal. Calc'd for $C_{15}H_{13}N_4O$: N, 21.20. Found: N, 21.59.

Synthesis of 2-(4'-arsonophenyl)-2,1,3-triazole. This synthesis was effected using the well known Bart procedure. In a typical run a solution of 20 g. (0.125 mole) of 2-(4'-aminophenyl)-2,1,3-triazole in 335 ml. of water containing 30 ml. (0.35 mole) of concentrated hydrochloric acid was diazotized at 0–5° by dropwise addition of 8.7 g. (0.125 mole) of sodium nitrite in 75 ml. of water. The mixture was stirred about 15 minutes after the addition was completed. To this diazonium salt solution was added a solution containing 22.3 g. of sodium hydroxide, 25 g. of arsenic trioxide, and 5.5 g. of cupric sulfate in 175 ml. of water. Nitrogen was evolved readily. This mixture was stirred 4 hours at 0°, and finally heated to 65°. It was then nearly neutralized with hydrochloric acid, and after adding decolorizing charcoal was filtered. To the filtrate was added hydrochloric acid until just acid to Congo Red. A light yellow solid formed which was crystallized twice from dilute acetic acid. The solid was nearly white. It did not melt when heated to 285°; yield of pure product 9.3 g. (27%).

Anal. Calc'd for $C_8H_8AsN_4O_3$: As, 27.84. Found: As, 27.56.

One attempt was made to reduce this compound to the corresponding arsine oxide using sulfur dioxide. The substance produced did not give a suitable analysis.

Attempted synthesis of 2-(4'-hydroxyphenyl)-2,1,3-triazole. Five different experiments were conducted in an attempt to prepare 2-(4'-hydroxyphenyl)-2,1,3-triazole. This compound might be of interest as an antiseptic. The basis of the attempted synthesis was to diazotize 2-(4'-aminophenyl)-2,1,3-triazole and to warm the diazonium salt as in the classical procedure for the replacement of the amino group with hydroxyl. Regardless of the conditions tried all these experiments resulted in failure.

Synthesis of 1-p-[8'-(2',1',3'-triazolyl)benzene-azo]-2-naphthol. To about 1 g. of 2-(4'-aminophenyl)-2,1,3-triazole was added hydrochloric acid and sodium nitrite under the usual conditions for diazotization. The diazonium salt solution was poured into a potassium hydroxide solution of beta-naphthol. A red precipitate formed which was washed thoroughly with water. The solid was placed in 60 ml. of 10% hydrochloric acid and allowed to stand 24 hours. The solid was filtered, washed thoroughly with water, and finally with ethanol. Since it was not very soluble in ethanol, it was not crystallized, but dried for analysis.

Anal. Calc'd for $C_{18}H_{13}N_3O$: N, 22.06. Found: N, 22.21.

Preparation of acetyl 2-(p-sulfanilamido)phenyl-2,1,3-triazole. A mixture of 11.7 g. (0.05 mole) of *p*-acetylaminobenzenesulfonyl chloride, 8 g. of 2-(4'-aminophenyl)-2,1,3-triazole, 100 ml. of water, and 10 ml. of pyridine was warmed just below the boiling point for 5 minutes. An oil first formed which gradually crystallized. This was crystallized from ethanol; yield 17 g. (95%), melting point 209–210°.

Anal. Calc'd for $C_{18}H_{15}N_3O_2S$: N, 19.59. Found: N, 20.57.

Preparation of 2-(p-sulfanilamido)phenyl-2,1,3-triazole. The 17 g. of the acetyl derivative from the preceding experiment was hydrolyzed by refluxing 3 hours in 7% hydrochloric acid solution. Refluxing was continued until all the product had dissolved. The solution was neutralized with sodium bicarbonate and the white solid which formed was crystallized from ethanol; yield 9.6 g. (64%), melting point 212–214°.

Anal. Calc'd for $C_{14}H_{11}N_3O_2S$: N, 23.49. Found: N, 22.82.

Preparation of p-2-(2,1,3-triazolyl)benzenesulfonamide. To 14.5 g. (0.10 mole) of 2-phenyl-2,1,3-triazole which was cooled to 0° was added 32 ml. of chlorosulfonic acid. The reaction was not so vigorous as observed with acetanilide. The mixture was warmed over steam 30 minutes, cooled, and poured slowly into ice-water. A white solid was formed which melted at 152–153°. It was assumed to be *p*-2-(2,1,3-triazolyl)benzenesulfonyl chloride and was used without further purification; yield 7 g. (40%). Four grams of the 2-phenyl-2,1,3-triazole was recovered. Better yields may be obtained by longer heating of the reaction mixture.

To 6 g. of the sulfonyl chloride produced above was added excess concentrated ammonium hydroxide. The mixture was warmed 15 minutes, water was added, and the white solid filtered. The solid was crystallized from ethanol. It melted at 245–247°; yield 4.5 g. (83%).

Anal. Calc'd for $C_{14}H_{11}N_3O_2S$: N, 24.94. Found: N, 24.66.

Preparation of p-2-(2,1,3-triazolyl)benzenesulfonanilide. To 2.4 g. (0.01 mole) of *p*-2-(2,1,3-triazolyl)benzenesulfonyl chloride was added 0.93 g. of aniline, 20 ml. of water, and a little pyridine. This mixture was warmed below the boiling point 10 minutes. Upon cooling, a solid formed which was crystallized from 95% ethanol; yield 1.7 g. (57%), melting point 163°.

Anal. Calc'd for $C_{14}H_{13}N_3O_2S$: N, 18.65. Found: N, 18.77.

Attempted preparation of 2-(4'-acetylphenyl)-2,1,3-triazole. A mixture was prepared containing 14.5 g. (0.1 mole) of 2-phenyl-2,1,3-triazole, 50 ml. of carbon disulfide, and 16 g. (0.12 mole) of anhydrous aluminum chloride. To this mixture was added 7.8 g. (0.10 mole) of acetyl chloride. Not much hydrogen chloride was evolved. The mixture was refluxed 30 minutes after addition was complete. The product was poured into ice-water containing hydrochloric acid, extracted with ether, the ether extract dried and distilled. Thirteen grams of the original 2-phenyl-2,1,3-triazole was recovered. In a similar experiment the refluxing was continued for 3 hours instead of 30 minutes but this resulted in

recovery of the original triazole with none of the expected compound. Nitrobenzene was substituted for carbon disulfide as a solvent but the results were still unfavorable.

PHARMACOLOGICAL STUDIES

A few of the compounds described above have been examined and a summary of the results follow.

2-(4'-Arsonophenyl)-2,1,3-triazole in aqueous solutions was administered orally and i. p. to mice infected with *T. equiperdum*, *T. gambiense* "V", and *Spirochaeta moryi* but no therapeutic activity was indicated in any instance. *In vitro* the arsonic acid was active on the above organisms in dilutions of 1:10,000 to 1:20,000 in egg slope medium and 1:20,000 to 1:50,000 in liquid liver medium.

2-(*p*-Sulfanilamido)phenyl-2,1,3-triazole was found to be ineffective in the treatment of mice infected with tetanus toxemia, or influenza virus, or rabic

TABLE I
ACTIVITY OF *p*-2-(2,1,3-TRIAZOLYL)BENZENESULFONANILIDE

No bactericidal action at 1-1,000		against <i>Staph. aureus</i> -209
No bactericidal action at 1-1,000		" <i>B. typhosus</i> -221
Bacteriostatic action at 1-1,000 but not at 1-5,000		" <i>Staph. aureus</i> -209
" action at 1-1,000 " " " 1-5,000		" <i>B. typhosus</i> -221
No fungicidal action at 1-1,000		" <i>T. interdigitale</i>
No " " " 1-1,000		" <i>T. rubrum</i>
No " " " 1-1,000		" <i>C. albicans</i>
Fungistatic " " 1-1,000 " " " 1-5,000		" <i>T. interdigitale</i>
" " " 1-1,000 " " " 1-5,000		" <i>T. rubrum</i>
No " " " 1-1,000		" <i>C. albicans</i>

virus. It was slightly effective in the treatment of mice infected with *Streptococcus hemolyticus*.

p-2-(2,1,3-Triazolyl)benzenesulfonanilide was tried against the organisms listed in table I and with the results indicated.

It was ineffective in the treatment of mice infected with *Streptococcus hemolyticus*, or tetanus toxemia, or influenza virus, or rabic virus.

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SUMMARY

1. A good method for the synthesis of 2-phenyl-2,1,3-triazole has been presented.

2. Eleven derivatives of this triazole have been prepared.

3. No therapeutic value has been suggested for any of the compounds with which pharmacological studies have been made.

ALBUQUERQUE, N. M.

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1-DODECANESULFINIC ACID

C. S. MARVEL AND RAYNER S. JOHNSON¹*Received May 12, 1948*

In connection with a study of aliphatic sulfinic acids as activators for Redox type polymerization (1) we have had occasion to prepare for the first time a pure crystalline aliphatic sulfinic acid, 1-dodecanesulfinic acid. Autenrieth (2) has reported the isolation of pure benzenesulfinic acid, but he found that the aliphatic acids were unstable, and did not accomplish their isolation. 1-Dodecanesulfinic acid appears to be considerably more stable than the lower alkanesulfinic acids but on standing for two months or on heating to 100° for a few hours it undergoes the disproportionation reaction reported for aliphatic sulfinic acids by von Braun and Weissbach (3) to yield 1-dodecyl 1-dodecanethiolsulfonate (I) and 1-dodecanesulfonic acid. When an excess of sulfur dioxide was used in the



preparation of the magnesium salt of the sulfinic acid from 1-dodecylmagnesium bromide by the procedure of Houlton and Tartar (4), the free sulfinic acid was formed and underwent disproportionation. The magnesium salt of the sulfinic acid was slowly oxidized in the air to the corresponding sulfonic acid salt.

We also investigated the Ziegler and Connor (5) cleavage of ethane disulfones by sodium cyanide as a route to the salts of the higher aliphatic sulfinic acids. This reaction gave a good yield of sodium 1-dodecanesulfinate but was unsatisfactory as a method of preparation of sodium 6-dodecanesulfinate.

1-Dodecanesulfinic acid reacted with 1-dodecanethiol in boiling ether to produce a high yield of 1-dodecyl 1-dodecanethiolsulfonate. von Braun and Weissbach (3) write the equation for the reaction of *n*-butanesulfinic acid and benzyl mercaptan as follows:

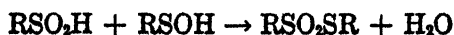


In the case of our reaction between 1-dodecanethiol and 1-dodecanesulfinic acid this equation does not seem to account for the products isolated. When equal molar quantities of the two reactants were used the yield of thiol ester was double that which should be obtained on the basis of the von Braun equation. Also when 0.02 mole of acid and 0.0067 mole of mercaptan were used the yield was more than twice that possible in the von Braun reaction. No dodecyl disulfide was obtained in either experiment. Heating the sulfinic acid under the same conditions in the absence of the mercaptan did not yield the thiolsulfonate.

These results support the views of Kharasch, Potempa, and Wehrmeister (6) that sulfinic acids are probable intermediates in reactions which involve sulfinic

¹ Allied Chemical and Dye Corporation Fellow 1947-48. Present address, Grasselli Chemicals Department, E. I. duPont de Nemours and Company, Wilmington, Delaware.

acids. The formation of thiolsulfonate from a free sulfinic acid has been attributed to the combination of two simpler reactions:



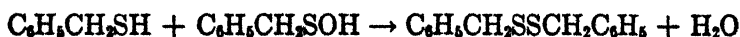
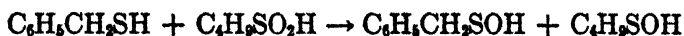
It is also reported that sulfenic acids disproportionate in similar fashion to give a number of products including disulfides.



Consideration of the above relations leads to the suggestion that a sulfinic acid could react with a mercaptan to yield a sulfenic acid.

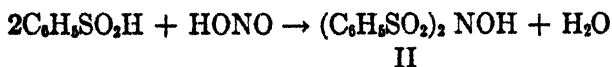


The products which von Braun and Weissbach isolated could then be explained by the following sequence of reactions:



If the combination of sulfenic acid with sulfinic acid to yield thiolsulfonate is more rapid than the reaction between sulfenic acid and mercaptan to give disulfide in the case of dodecyl derivatives, these reactions would account for the yields and the products which we have obtained in our experiments.

Koenigs (7) reported that nitrous acid converts benzenesulfinic acid to N,N-di(benzenesulfonyl)hydroxylamine (II).



Since we were using nitrous acid titration to determine the sulfinic acid content of our various materials (2) we have determined the products of the reaction in the case of 1-dodecanesulfinic acid. When exactly equivalent amounts of nitrous acid and sulfinic acid were used, the principal product of the reaction was N,N-di(1-dodecanesulfonyl)hydroxylamine (III) with a trace of a by-product tri-(1-dodecanesulfonyl)amine oxide (IV). When an excess of nitrous acid was used with the sulfinic acid, the amine oxide derivative (IV) became the major product.



Treatment of the hydroxylamine derivative with nitric acid in glacial acetic acid also gave the amine oxide derivative. Zuckschwerdt (8) and Koenigs (9) have reported similar amine oxide derivatives by treatment of aliphatic and

aromatic sulfinic acids with fuming or concentrated nitric acid. We have observed that the hydroxylamine derivative (III) decomposes on standing at room temperature to yield the amine oxide derivative (IV) and oxides of nitrogen.

In seeking a solid derivative for the identification of 1-dodecanesulfinic acid we have treated its sodium salt with chloroacetic acid and thus obtained 1-dodecanesulfonyl acetic acid which is easily purified and melts sharply at 108–109°.

EXPERIMENTAL

1-Dodecanesulfinic acid. The Grignard reagent prepared from 125 g. (0.5 mole) of 1-bromododecane in 500 cc. of ether was treated with 32 g. (0.5 mole) of sulfur dioxide at -40° to -35° as described by Houlton and Tartar (4a) and Allen (4b). The reaction mixture was poured into a cold aqueous ammonium chloride solution and the insoluble magnesium 1-dodecanesulfinate was thoroughly washed with water. The salt was air dried and extracted with ether and with carbon tetrachloride. Evaporation of the ether extracts yielded 8 g. of a waxy hydrocarbon which melted at $51-51.5^{\circ}$ after crystallization from 95% ethanol. Krafft (10) has reported the melting point of *n*-tetracosane as 51.1° . The magnesium salt was further washed thoroughly with hot 95% ethanol to remove any magnesium 1-dodecanesulfonate. The yield of magnesium 1-dodecanesulfinate dihydrate thus obtained was 105 g. (80%).

Two grams of freshly prepared magnesium 1-dodecanesulfinate dihydrate was ground to a fine powder and extracted first with two 50-cc. portions of boiling 95% ethanol and then with two 50-cc. portions of diethyl ether. The remaining powder was shaken with 100 cc. of 2% aqueous hydrochloric acid and 50 cc. of diethyl ether. The ether layer was separated, washed with two 100-cc. portions of water and filtered. The ether was distilled under reduced pressure and the crystalline residue was dried in a desiccator at 0.15 mm. pressure. The yield was 1.7 g. (96%) of 1-dodecanesulfinic acid, m.p. $29-30^{\circ}$. The material was analyzed within twenty-four hours of its preparation.

Anal. Calc'd for $C_{12}H_{24}O_2S$: C, 61.49; H, 11.18; S, 13.75.

Found: C, 61.92; H, 11.36; S, 13.66.

Conversion of 1-dodecanesulfinic acid to 1-dodecyl 1-dodecanethiolsulfonate. A 1-g. sample of pure sulfinic acid, m.p. $29-30^{\circ}$, was allowed to stand in a stoppered bottle at room temperature ($22-25^{\circ}$). The solid gradually changed to an oil and was completely liquid in two weeks. After a month of standing the oil began to resolidify and in two months it became completely solid, m.p. $37-40^{\circ}$. A sample of this material recrystallized from ethanol melted at $42-44^{\circ}$ and did not depress the melting point of a known sample of 1-dodecyl 1-dodecanethiolsulfonate (see below).

The free sulfinic acid from 5.3 g. of magnesium 1-dodecanesulfinate dihydrate was heated in a nitrogen atmosphere on a steam-bath for two and one-third hours. The dark oily material thus obtained was poured into a solution of 1 g. of sodium acetate in 200 cc. of water. The portion insoluble in water was extracted with ether, the ether solution treated with decolorizing carbon (Norit) and the solvent was removed. The white crystalline residue was recrystallized from 95% ethanol, m.p. $41-42^{\circ}$. A mixture with an authentic sample of 1-dodecyl 1-dodecanethiolsulfonate melted at the same temperature. The yield was 2 g. (69%). The above aqueous sodium acetate solution was evaporated to dryness and the solid residue recrystallized from 95% ethanol to give 1 g. of sodium 1-dodecanesulfonate (identified as a sulfur containing salt which did not react with sodium nitrite solution).

Air oxidation of magnesium 1-dodecanesulfinate. A sample of dry powdered magnesium 1-dodecanesulfinate dihydrate was exposed on a watch glass and the sulfinate content was checked during one hundred nineteen days by titrating with 0.1 normal nitrite solution. The results are summarized in Table I.

A sample of unpurified magnesium 1-dodecanesulfinate (85% sulfinate by nitrite titra-

tion) was allowed to stand in an open dish for six months. Nitrite titration showed that only a trace of sulfinate remained. The magnesium salt was soluble in hot water and hot 95% ethanol. These are properties of the sulfonate and not the sulfinate.

Reaction of excess sulfur dioxide with 1-dodecanemagnesium bromide. The Grignard reagent prepared from 200 g. of 1-bromododecane was treated at about -35° with approximately a three-fold excess of sulfur dioxide over that required to yield the salt of the sulfinic acid. Hydrolysis of this reaction mixture with cold aqueous ammonium chloride solution and isolation of the product as before gave 100 g. of solid melting at $39-41^{\circ}$. Crystallization of a sample from chloroform gave a small amount of tetracosane, m.p. $51-52^{\circ}$. The chloroform solution fraction was recrystallized from low-boiling petroleum ether to give a solid m.p. $44-45^{\circ}$ which proved to be 1-dodecyl 1-dodecanethiolsulfonate.

Anal. Calc'd for $C_{24}H_{50}O_2S_2$: C, 66.30; H, 11.59.

Found: C, 66.73; H, 11.82.

Hydrolysis of 35 g. of the crude ester with 10 g. of sodium hydroxide in 400 cc. of 95% ethanol at the boiling point for three hours gave 16 g. of sodium 1-dodecanesulfinate. Titration with standard nitrite indicated the salt was at least 86% sulfinate.

Anal. Calc'd for $C_{12}H_{24}NaO_2S$: C, 56.24; H, 9.83; Na, 8.97.

Found: C, 56.30; H, 9.99; Na, 8.88.

TABLE I
AIR OXIDATION OF MAGNESIUM 1-DODECANESULFINATE

DAYS OF STANDING	% SULFINATE CONTENT
0	96
25	89
54	82
91	74
119	66

1,2-Bis(1-dodecylthio)ethane. The procedure used was a modification of that described by Ziegler and Connor (5) for the *n*-butyl analog. In a 1-liter three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and dropping-funnel was placed 150 cc. of absolute ethanol. Six grams (0.26 g. atom) of sodium was added in small pieces followed by 50.5 g. (0.25 mole) of *n*-dodecyl mercaptan. The mixture was brought to reflux temperature, the source of heat withdrawn, and a solution of 18.8 g. (0.1 mole) of ethylene bromide in 100 cc. of absolute ethanol added with stirring at such a rate that moderate refluxing was maintained. The addition was complete in one-half hour and the mixture was then heated under reflux for four hours. When the reaction mixture was cooled, a solid crystallized which was washed with water, and extracted with diethyl ether. The insoluble salt was removed, the ether distilled under diminished pressure, and the residue recrystallized twice from absolute ethanol, m.p. $54-55^{\circ}$; the yield was 35 g. or 81%.

Anal. Calc'd for $C_{26}H_{54}S_2$: C, 72.48; H, 12.64.

Found: C, 72.30; H, 12.63.

1,2-Bis(1-dodecylsulfonyl)ethane. A solution of 30 g. (0.07 mole) of 1,2-bis(1-dodecylthio)ethane in 1200 cc. of glacial acetic acid was warmed to 70° and a solution of 44 g. (0.28 mole) of potassium permanganate in 400 cc. of water was slowly added with stirring. The reaction was complete in about fifteen minutes, and the mixture was cooled to 25° . The solid precipitate was washed with water, suspended in 1500 cc. of ice water, and bleached with sulfur dioxide. The white solid was washed with a large quantity of water, dried at room temperature, and extracted with warm diethyl ether. The yield of the insoluble material which melted at $160-161^{\circ}$ was 28 g. or 81%. A sample was recrystallized from a glacial acetic acid-absolute ethanol mixture, m.p. $161-162^{\circ}$ ($165-166^{\circ}$ corr.).

The melting point of 1,2-bis(1-dodecylsulfonyl)ethane prepared by a different procedure is reported in the literature (4b) at 165.8–166.8°.

Anal. Calc'd for $C_{24}H_{48}O_4S_2$: C, 63.15; H, 10.93.

Found: C, 63.03; H, 10.99.

Hydrolysis of 1,2-bis(1-dodecylsulfonyl)ethane. A modification of the method of Ziegler and Connor (5) was used. In a 3-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser and dropping-funnel were placed 1200 cc. of 95% ethanol and 24.7 g. (0.05 mole) of 1,2-bis(1-dodecylsulfonyl)ethane. The mixture was heated under reflux and a solution of 16.5 g. (0.25 mole) of potassium cyanide in 70 cc. of water was added with stirring. After the mixture was refluxed for thirty minutes, all of the disulfone had gone into solution. An additional 100 cc. of water was added, and the solution stirred and heated under reflux for twenty hours. Most of the solvent was removed by distillation under diminished pressure, leaving about 200 cc. of liquid residue.

The reflux condenser was replaced by an outlet tube which was connected through a sodium hydroxide trap to a water-pump. The cold residue was then acidified under diminished pressure by slow addition of a solution of 40 cc. of concentrated hydrochloric acid in 300 cc. of water. The acidified residue was extracted with 300 cc. of ether and the ether evaporated under diminished pressure to remove any remaining hydrogen cyanide. The residue, which was a solid below room temperature, was then dissolved in 100 cc. of absolute ethanol and added to a solution of 4 g. (0.1 mole) of sodium hydroxide in 400 cc. of 95% ethanol. A solid immediately crystallized and the mixture was cooled to 0°. After recrystallization from ethanol the yield of sodium 1-dodecanesulfinate monohydrate was 22 g. or 80%. The analysis of this material by nitrite titration showed a 92% sulfinate content.

1,2-Bis(6-dodecylthio)ethane. In a 1-liter, three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and dropping-funnel were placed 14.7 g. (0.066 mole) of 90% 6-dodecyl mercaptan,² 5.6 g. (0.03 mole) of ethylene bromide, and 100 cc. of 95% ethanol. The mixture was heated under reflux and with stirring, and a solution of 1.8 g. of sodium in 50 cc. of 95% ethanol was added over the period of one hour. After stirring and refluxing the resulting solution for an additional hour, it was concentrated to 50 cc. by removal of the solvent under diminished pressure. To this concentrate was added 100 cc. of water and the mixture extracted with three 50-cc. portions of low-boiling petroleum ether. The extracts were combined, dried over sodium sulfate, and the ether distilled under diminished pressure, leaving 15.3 g. of clear oily residue.

A 12.8-g. sample of the crude oil product was distilled through an electrically heated 10-in. Vigreux column to give a fraction of 10.3 g., b.p. 170–180° (0.1 mm.); n_D^{20} 1.4808. Redistillation of this fraction gave 7.5 g. of liquid which boiled at 180° (0.1 mm.); n_D^{20} 1.4818. The yield of 1,2-bis(6-dodecylthio)ethane thus obtained was 70%.

Anal. Calc'd for $C_{24}H_{48}S_2$: C, 72.48; H, 12.64.

Found: C, 72.73; H, 12.58.

1,2-Bis(6-dodecylsulfonyl)ethane. A mixture of 2 g. (0.0046 mole) of 1,2-bis(6-dodecylthio)ethane and 50 cc. of glacial acetic acid was warmed to 45° and 3 g. (0.019 mole) of potassium permanganate in 30 cc. of solution added with stirring at this temperature over a period of one hour. The mixture was then treated with sulfur dioxide and the clear oil layer extracted with low-boiling petroleum ether. The ether was removed by distillation under diminished pressure leaving a liquid residue which solidified at about 5°. After several recrystallizations from methanol, the solid melted at 23–24°. The yield of the thus purified product was 1.7 g. or 74%.

Anal. Calc'd for $C_{24}H_{48}O_4S_2$: C, 63.15; H, 10.93.

Found: C, 62.70; H, 10.88.

² This material is believed to be contaminated with 6-bromododecane. See Frank, Smith, Woodward, Reynolds, and Canterino, *J. Polymer Sci.*, in press.

Hydrolysis of 1,2-bis(6-dodecylsulfonyl)ethane. The procedure was the same as that described for the hydrolysis of 1,2-bis(1-dodecylsulfonyl)ethane. From 1.5 g. (0.003 mole) of 1,2-bis(6-dodecylsulfonyl)ethane was obtained 1.6 g. of the crude sodium sulfinate as an amorphous solid. Purification of this salt was not successful. It was shown to be only 35% sulfinate by nitrite titrations.

Action of 1-dodecanethiol on 1-dodecanesulfinic acid. A mixture of 5.3 g. (0.01 mole) of freshly prepared magnesium 1-dodecanesulfinate dihydrate, 100 cc. of 5% hydrochloric acid, and 75 cc. of ether was shaken in a separatory funnel until all of the solid had dissolved. The ether extract was transferred to a flask equipped with a mechanical stirrer and reflux condenser and containing 2 g. (0.01 mole) of 1-dodecanethiol. The mixture was stirred and heated under reflux for one hour and an additional 2 g. (0.01 mole) of 1-dodecanethiol along with two drops of concentrated hydrochloric acid was added. After this mixture had been stirred and heated under reflux for fifteen hours, the ether solvent was removed under diminished pressure, leaving a residue of white solid along with a small amount of oil. The solid was isolated by crystallization from 500 cc. of 95% ethanol, m.p. 43–44°. A mixed melting point with a sample of 1-dodecyl 1-dodecanethiolsulfonate previously identified was not depressed. The yield was 5.6 g.

Anal. Calc'd for $C_{21}H_{40}O_2S_2$: C, 66.30; H, 11.59.

Found: C, 66.51, 66.61; H, 11.37, 11.58.

The alcohol filtrate obtained above was evaporated under diminished pressure, leaving an oil residue which was treated with 50 cc. of 5% sodium carbonate solution and the insoluble oil extracted with ether. The ether left an oil which distilled at 255–265°; n_D^{20} 1.4585. An authentic sample of 1-dodecanethiol was found to distill at 260–265° under the same conditions, n_D^{20} 1.4588. The amount of recovered 1-dodecanethiol was 1.5 g. From the quantity of thiol consumed, the theoretical yield of the thiolsulfonate based upon the equation of von Braun and Weissbach (3) is 2.7 g.

Another run was made using a 3:1 mole ratio of sulfinic acid and mercaptan. From 5.3 g. (0.01 mole) of the magnesium salt and 1.35 g. (0.0067 mole) of 1-dodecanethiol, 3.2 g. of 1-dodecyl 1-dodecanethiolsulfonate was obtained, m.p. 41.5–43°. The theoretical yield by the mechanism of von Braun and Weissbach (3) should be 1.45 g. based on the amount of mercaptan used.

In order to determine if any of the thiolsulfonate had been formed by disproportionation of the sulfinic acid, another run was made. The sulfinic acid, obtained from 5.3 g. (0.01 mole) of the magnesium salt by the same procedure as above, was heated in refluxing ether for sixteen hours with two drops of concentrated hydrochloric acid, but with no mercaptan. The ether was then distilled under diminished pressure as before, leaving a solid residue which melted below room temperature into a clear oil. This oil dissolved in 100 cc. of 5% sodium carbonate with evolution of carbon dioxide, and no insoluble thiolsulfonate was obtained. The solution was evaporated to dryness on a steam cone and the residue extracted with 95% ethanol. The extract was cooled, and yielded 4.1 g. of solid which showed 90% sulfinate by the usual nitrite titration.

N,N-Di(1-dodecylsulfonyl)hydroxylamine. To a solution prepared from 10 cc. of concentrated hydrochloric acid, 60 cc. of water, and 200 cc. of glacial acetic acid was added 2.6 g. (0.005 mole) of freshly prepared magnesium 1-dodecanesulfinate dihydrate. The mixture was shaken at 0° until all of the salt was in solution, and titrated at that temperature with 0.1 normal sodium nitrite. When the end point was reached, using an outside indicator of starch-potassium iodide paper, the addition was stopped. The white solid which crystallized during the nitrite addition was washed with about 1000 cc. of water, and dried. The solid was recrystallized from low-boiling petroleum ether, m.p. 72–74°. The yield of 2.5 g. was quantitative.

The same product was obtained by a procedure similar to that described by Koenigs (7). A solution of 16.5 g. (0.06 mole) of sodium 1-dodecanesulfinate monohydrate and 4.2 g. (0.06 mole) of sodium nitrite in 1000 cc. of water was acidified at 20° with dilute hydrochloric acid. The solid product was washed with water, and dried. After recrystallization

from petroleum ether the solid melted at 74–75°. The yield was 12.5 g. or 84% of the theoretical amount. A sample was recrystallized from ethanol, m.p. 76–77°.

Anal. Calc'd for $C_{24}H_{48}NO_3S_2$: C, 57.91; H, 10.33; N, 2.81.

Found: C, 58.02; H, 10.53; N, 2.92.

When only one-half of the equivalent amount of sodium nitrite was added to the dodecanesulfinic acid in acetic acid solution using the titration procedure previously described, a quantitative yield, based on the sodium nitrite used, of the above product was obtained in almost pure form, m.p. 74–75°. Using the same titration procedure, when the sulfinic acid was titrated to the end point with nitrite, the product melted at 72–74° as reported above, and when an excess of nitrite was added, the product melted at 60–70°.

Tri(1-dodecylsulfonyl)amine oxide. A solution of 50 cc. of glacial acetic acid and 1.6 g. (0.003 mole) of freshly prepared N,N-di(1-dodecylsulfonyl)hydroxylamine, m.p. 72–74°, was warmed to 45°, and 5 cc. of concentrated nitric acid (d. 1.42) was added with stirring in about five minutes. The flask was stoppered and allowed to stand at room temperature for ten hours. The mixture was then cooled and the solid which had crystallized was washed with a small amount of cold 80% acetic acid. The yield of the dry product, m.p. 60–61°, was 0.4 g. After recrystallization from 90% acetic acid, it melted at 61–62°.

Anal. Calc'd for $C_{36}H_{72}NO_7S_3$: C, 59.22; H, 10.35; N, 1.92.

Found: C, 59.57, 59.35; H, 10.23, 10.40; N, 2.04.

The N,N-di(1-dodecylsulfonyl)hydroxylamine was also oxidized to the amine oxide by the action of an excess of nitrous acid at about 50°. The product was more difficult to purify in this case and after several recrystallizations from ethanol and petroleum ether, it melted at 58–59°. A mixed melting point with the product obtained by nitric acid oxidation was not depressed. A sample of the solid hydroxylamine derivative was also found to decompose spontaneously at room temperature with the evolution of red-brown nitrogen oxides. The amine oxide, m.p. 60–61° was isolated from the decomposition product.

O-Acetyl N,N-di(1-dodecylsulfonyl)hydroxylamine. One gram (0.002 mole) of N,N-di(1-dodecylsulfonyl)hydroxylamine was added to 25 cc. of acetic anhydride and the solution stirred for one-half hour. The solution was then warmed to 100° with stirring over a period of one-half hour, allowed to cool, and poured into water. After the acetic anhydride was hydrolyzed, the solid residue was recrystallized from 80% acetic acid, m.p. 45–46°. The yield was 0.7 g. or 65%. After further recrystallization from 80% acetic acid the solid melted at 47–48°.

Anal. Calc'd for $C_{26}H_{52}NO_6S_2$: C, 57.85; H, 9.90; N, 2.60.

Found: C, 57.81; H, 10.08; N, 2.66.

1-Dodecylsulfonylacetic acid. The procedure was similar to that described by Gabriel (11). A solution of 1.9 g. (0.02 mole) of monochloroacetic acid in 150 cc. of water was neutralized with 1.7 g. (0.02 mole) of sodium bicarbonate and then treated with a solution of 5.8 g. (0.02 mole) of sodium 1-dodecanesulfinate monohydrate in 100 cc. of water. The mixture was evaporated to about 100 cc. with an open flame, then placed in an evaporating dish and evaporated to dryness on a steam cone. The solid residue was dissolved in 300 cc. of hot water and on cooling, the sodium salt crystallized; the yield was 5.4 g. or 85%.

The sodium salt was dissolved in hot water, neutralized with dilute hydrochloric acid, and the solid which precipitated was recrystallized from an ethanol-water mixture, m.p. 107–109°. It was then recrystallized from high-boiling petroleum ether, m.p. 108–109°. The yield was 4.3 g. or an over-all yield of 74%. After recrystallization from glacial acetic acid, the solid still melted at 108–109°.

Anal. Calc'd for $C_{14}H_{28}O_3S$: C, 57.50; H, 9.65.

Found: C, 57.42; H, 9.47.

SUMMARY

Crystalline 1-dodecanesulfinic acid has been isolated and characterized. On standing, it disproportionates to 1-dodecyl 1-dodecanethiolsulfonate and 1-do-

decanesulfonic acid. On standing in air, the magnesium sulfinic acid oxidizes to the sulfonate. The reaction of 1-dodecanethiol and 1-dodecanesulfinic acid to give 1-dodecyl 1-dodecanethiolsulfonate has been examined and on the basis of yields it is suggested that 1-dodecanesulfinic acid may be an intermediate in this reaction.

The reaction of nitrous acid with 1-dodecanesulfinic acid has been found to yield di-(1-dodecanesulfonyl)hydroxylamine and tri-(1-dodecanesulfonyl)amine oxide.

1-Dodecanesulfonylacetic acid prepared from sodium 1-dodecanesulfinate and chloroacetic acid is a good derivative for characterization of the sulfinic acid.

URBANA, ILL.

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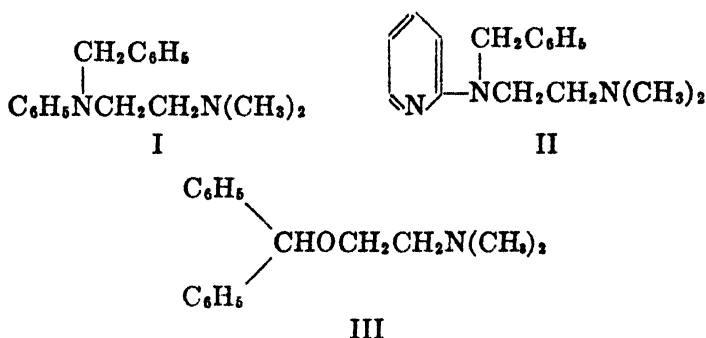
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2-(BENZHYDRYLOXYMETHYL)IMIDAZOLINE, A NEW HISTAMINE ANTAGONIST

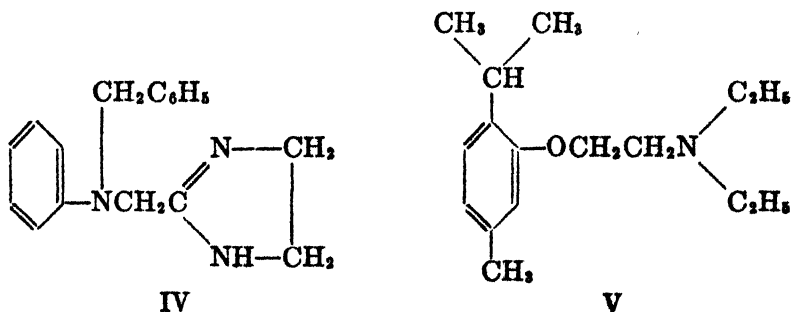
CARL DJERASSI AND CAESAR R. SCHOLZ

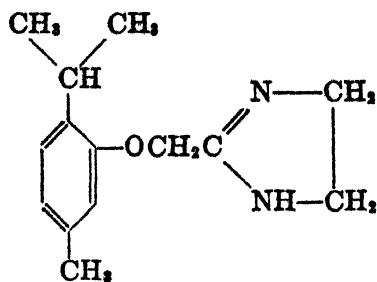
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Most of the recently published work on antihistaminic drugs centered on preparing a variety of compounds derived from *N,N*-dimethylethylenediamine (1, 2) and β -dimethylaminoethanol (3), which resulted in the discovery of therapeutically active drugs such as Antergan (I) (1), Pyribenzamine (II) (2) and Benadryl (III) (3).



Miescher, Klarer, and Urech (4) were able to show, however, that the dimethylaminoethyl moiety is not entirely essential for antihistaminic activity, since 2-*N*-benzyl-*N*-phenylaminomethylimidazoline (Antistine) (IV) has strong histaminolytic properties and differs from Antergan (I) only in the nature of the side chain. Recently (5), we have extended the scope of this observation by preparing imidazoline and amidine analogs of phenolic ethers, such as F929 (V), which have been synthesized in Fourné's laboratory and which were among the first specific histamine antagonists (6). We found the 2-(thymoxymethyl)imidazoline (VI) to be at least as active as V and therefore we have continued our work on the replacement of the dialkylaminoethyl side chain of various pharmacologically active compounds by other substituents such as the 2-methylimidazoline group.



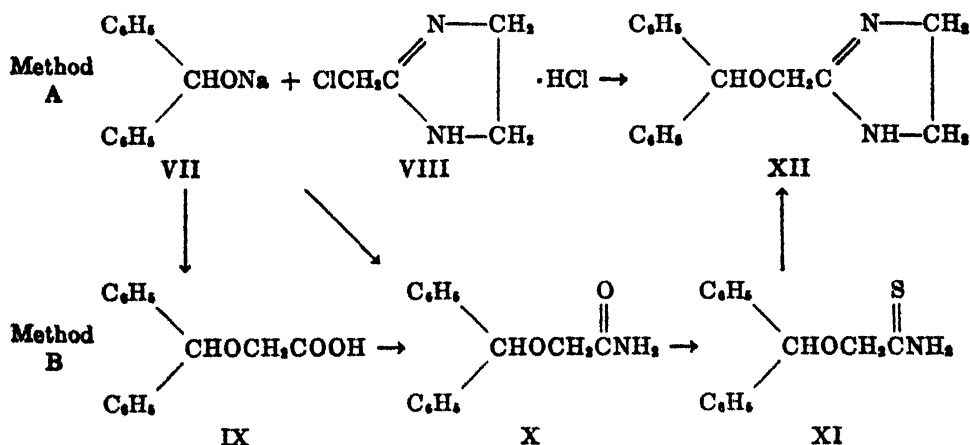


VI

On applying this approach to β -dimethylaminoethyl benzhydryl ether (III) (3), we have synthesized 2-(benzhydryloxymethyl)imidazoline (XIII) and have found it to be a strong histamine antagonist. The present paper, which deals with the synthesis of this compound, is prompted by the appearance of a preliminary note by Cavallini and Mazzuchi (7) who reported some of the physical constants and pharmacological data of this substance, but did not record the method of synthesis.

Of a number of syntheses which have been studied, the following two have proved to be the most satisfactory. Method A involved the direct condensation of sodium benzhydrylate (VII) and 2-(chloromethyl)imidazoline hydrochloride (VIII) (8) in toluene suspension, while Method B employed as the key intermediate benzhydryloxyacetamide (X), which after Kindler conversion (9) to the thioamide (XI) and reaction with ethylenediamine according to Forssell (10) afforded the desired imidazoline XII. The melting points of the base, its picrate and hydrochloride agree well with the values reported by the Italian workers (7).

Since the submission of this paper, an article by Dahlbom and Sjögren (11) has come to our attention in which the preparation of the imidazoline XII by method A is described.



The detailed pharmacological results on this imidazoline derivative XII will be published by Dr. B. N. Craver and co-workers from our Division of Macro-

biology. Briefly, compound XII was about one-half as toxic as Pyribenzamine (II) (2) in rats (L.D.₅₀ intravenous = 23 mg./kg.) and demonstrated antihistaminic and antianaphylactic properties *in vitro* and in guinea pigs, comparable to those of Benadryl and Pyribenzamine. Contrary to the action of some antihistaminic drugs, this substance *per se* relaxes the bronchiolar muscles of the guinea pig.

EXPERIMENTAL¹

2-(Benzhydryloxy)methylimidazoline (XII). *Method A.* Since our procedure is essentially the same as that of the Swedish investigators (11), the experimental details are not repeated here except for the following physical constants:

2-(Benzhydryloxy)methylimidazoline (XII) was obtained as colorless needles from hexane-acetone and melted at 102–103° [lit. (7, 11): 102–103°].

Anal. Calc'd for $C_{17}H_{18}N_2O$: N, 10.52. Found: N, 10.56.

The hydrochloride formed colorless, non-hygroscopic crystals from a mixture of ethanol and methyl ethyl ketone and showed the m.p. 207–208° [reported (7): 204–205°; (11): 203–205°].

Anal. Calc'd for $C_{17}H_{19}ClN_2O$: N, 9.25; HCl, 12.32.

Found: N, 9.39; HCl, 12.27.

The picrate crystallized from acetone as bright yellow prisms, m.p. 204–205° [lit. (7); 205°; (11): 202–204°; no analysis was given].

Anal. Calc'd for $C_{22}H_{21}N_5O_8$: C, 55.75; H, 4.27; N, 14.14.

Found: C, 55.66; H, 4.34; N, 14.00.

Benzhydryloxyacetic acid (IX). The apparatus consisted of a ground-joint, three-necked flask equipped with mercury seal, Hershberg stirrer, combined gas inlet tube, and dropping-funnel, and in the third side arm a Vigreux column with sealed-on condenser set downward for distillation. A solution of 3.4 g. of sodium in 60 cc. of methanol was treated in a current of nitrogen while stirring with a solution of 27.6 g. of benzhydrol in 120 cc. of dry toluene. The clear solution was immersed in an oil-bath maintained at ca. 140–150° so that a moderate rate of distillation was achieved. Sodium benzhydrolate started to appear after a short time and dry toluene was added from time to time so as to keep the reaction mixture fluid until the temperature in the Vigreux column had reached 90°. The column was then replaced by a reflux condenser and 10.4 g. of bromoacetic acid was added followed by 70 cc. of toluene. After refluxing with stirring under nitrogen for one and one-half hours, water was added, the solution made alkaline and the toluene was removed by steam distillation. The residue was extracted with ether to recover unreacted benzhydrol (15.5 g.), and the alkaline solution acidified and again extracted with ether. The ether solution was washed until neutral, dried, evaporated, and the residue recrystallized from hexane-acetone to yield 11.5 g. (63%) of colorless crystals of the acid IX melting at 77–79°.

Anal. Calc'd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82; neut. equiv. 242.

Found: C, 74.18; H, 5.87; neut. equiv. 244.

A sample of the acid on treatment with ethereal diazomethane solution, evaporation, and crystallization from hexane gave methyl benzhydryloxyacetate melting at 37–39°.

Anal. Calc'd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29.

Found: C, 74.70; H, 5.93.

The ethyl ester, prepared from sodium benzhydrolate and ethyl bromoacetate, was obtained as a heavy oil, b.p. 170–180° at 1 mm., n_D^{20} 1.5500.

Anal. Calc'd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71.

Found: C, 75.80; H, 6.68.

¹ All melting points are corrected. The microanalyses were carried out by Mr. Joseph Alicino, Metuchen, N. J. The Misses Helen Dudek and Jean Rogers assisted capably in the experimental work.

Benzhydroxyacetamide (X). A solution of 4.8 g. of the acid IX in 30 cc. of benzene was refluxed with 4 cc. of thionyl chloride and two drops of pyridine for one-half hour and excess thionyl chloride was removed by repeated addition of benzene and distillation to dryness under reduced pressure. The residue was redissolved in benzene and added to an ethanolic ammonia solution. After removal of the solvent, the material was taken up in acetone, filtered, and hexane was added, whereupon the amide crystallized as colorless needles, m.p. 135.5–136°; yield 3.8 g. (76%). Recrystallization from ethanol did not change the melting point. The same product was obtained by shaking a suspension of methyl or ethyl benzhydroxyacetate with concentrated aqueous ammonium hydroxide solution overnight, or by condensing sodium benzhydrolate (VII) with chloroacetamide.

Anal. Calc'd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81.

Found: C, 74.69; H, 6.28; N, 6.02.

2-(Benzhydroxymethyl)imidazoline (XII). *Method B.* The Kindler reaction (9) was carried out by stirring 2.4 g. of the amide X, 0.9 g. of phosphorus pentasulfide, 0.62 g. of powdered anhydrous sodium sulfide, and 10 cc. of toluene until a homogeneous paste was obtained, and then heating with stirring at 80–90° for one-half hour. The mixture was cooled, the supernatant liquid was decanted and the residue stirred with 10 cc. of toluene at 80° for fifteen minutes and the process repeated. The combined toluene solutions were concentrated and diluted with hexane to yield 2.74 g. of material melting at 96–104° (turbid); on dissolving in acetone, filtering, and adding hexane, the crystals melted at 102–105° and represented an approximately 1:1 mixture (Found: S, 6.99) of *thioamide* XI and amide X. This crop was subjected directly to the Forssell procedure (10) by refluxing with a slight excess of anhydrous ethylenediamine (based on total amide mixture) in toluene solution for three hours. After working up as in method A by extracting with acid, there was obtained a nearly quantitative yield of recovered amide X from the neutral fraction, while the basic fraction gave 57–68% of 2-(benzhydroxymethyl)imidazoline (XII) characterized as the hydrochloride and picrate.

SUMMARY

Two methods for the preparation of a new histamine antagonist, 2-(benzhydroxymethyl)imidazoline (XII), have been described. Preliminary pharmacological data are included.

SUMMIT, NEW JERSEY

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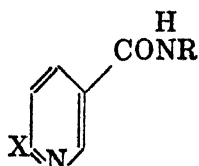
EXPERIMENTAL CHEMOTHERAPY OF TUBERCULOSIS.

I. SUBSTITUTED NICOTINAMIDES

S. KUSHNER, HARRY DALALIAN, ROBERT T. CASSELL,¹ J. L. SANJURJO,
D. MCKENZIE, AND Y. SUBBAROW

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Experimental *in vivo* investigations in our laboratories have shown that many compounds may have tuberculostatic activity. One of these, nicotinamide (I), showed considerable promise and this nucleus was subjected to a two-fold variation. Derivatives of type II were prepared, wherein the amide group was substituted and the ring kept constant. Compounds of this type had some activity but far less than that of free nicotinamide. Of these compounds the most active was *N*-(2-thiazolyl)nicotinamide, but it was too toxic for further use.



- I R, X = H
 II R = C₆H₇..., heterocycle, etc. X = H
 III R = H, X = Cl, NH₂, C₆H₅O, etc.

Compounds of type III were prepared where the amide group was unchanged and ring substitution made. These showed no activity. Many of the compounds used as intermediates in this investigation such as *p*-aminosalicylic acid and 5-amino-2-methylcoumarane (1) which were by themselves active, lost their activity completely when converted to the corresponding nicotinamide.

Evidence presented elsewhere (2) supports the belief that the role of nicotinamide in the treatment of experimentally infected mice is that of a vitamin.

Acknowledgment. The authors wish to thank Mr. L. Brancone and staff for the microanalyses recorded within.

EXPERIMENTAL

N-Nicotinyl-3-aminopyridine. To a solution of 15 g. (0.16 mole) of 3-aminopyridine and 30 ml. of pyridine was cautiously added 23 g. (0.16 mole) of nicotinyl chloride. After heating for fifteen minutes the reaction mixture was poured onto ice-water, filtered, and washed with water; wt. 21 g., m.p. 186°. After one recrystallization from alcohol it melted at 188°.

Nicotinyl-dicyandiamide. To a stirred (25–30°) solution of 15 g. (0.18 mole) of dicyandiamide, 20 g. (0.5 mole) of 95% sodium hydroxide, 75 ml. of water, and 75 ml. of acetone was added dropwise 30 g. (0.21 mole) of nicotinyl chloride. A further addition of 20 ml. of water was made and the reaction mixture was acidified with acetic acid. The product was filtered and washed, wt. 12 g. After recrystallization from 50% alcohol it melted at 170–175°.

p-(Nicotinylamino)benzoic acid. To a continuously stirred cold solution of 7 g. (0.18 mole) of sodium hydroxide, 20 g. (0.15 mole) of *p*-aminobenzoic acid, and 300 ml. of water

¹ Present address, Medical School, University of Geneva, Geneva, Switzerland.

TABLE I
 SUBSTITUTED NICOTINAMIDES

NO.	PRODUCT	METHOD OF PREPARATION	M.P., °C.	FORMULA	CALCULATED			FOUND			ACTIVITY
					C	H	N	C	H	N	
1	N-nicotinyl-3-amino-pyridine	A	188	C ₁₁ H ₉ N ₂ O	66.3	4.5	21.1	66.9	5.0	21.1	+
2	N-nicotinyl-2-amino-pyridine (3)	A	141-143	C ₁₁ H ₉ N ₂ O			21.1			21.1	-
3	N-nicotinyl-1-amino-anthraquinone	A	205	C ₂₀ H ₁₂ N ₂ O ₂	73.2	3.7	8.5	73.3	3.9	8.6	-
4	N-(2-thiazolyl)nicotinamide	A	211 dec.	C ₉ H ₇ N ₃ OS			20.5			20.6	++
5	N-cyclohexylnicotinamide (3)	A	140-142	C ₁₂ H ₁₆ N ₂ O			13.7			13.8	-
6	N-dodecoylnicotinamide (3)	A	63- 64.5	C ₁₄ H ₂₆ N ₂ O			9.7			9.3	-
7	5-(Nicotinylamino)-2-methylcoumarane	A	140	C ₁₈ H ₁₄ N ₂ O ₂	70.9	5.5	11.0	70.2	5.9	10.5	-
8	Nicotinyl-dicyandiamide	A	170-175	C ₈ H ₇ N ₅ O			37.3			37.5	-
9	N-nicotinylbenzylamine	A	125-126	C ₁₃ H ₁₂ N ₂ O			13.2			13.2	-
10	4-(Nicotinylamino)salicylic acid	A	195 dec.	C ₁₃ H ₁₀ N ₂ O ₄	60.5	3.9	10.9	60.3	4.0	11.2	-
11	N-nicotinyl-2-amino-5-azoisole	A	150-152	C ₂₀ H ₁₄ N ₄ O ₂	66.3	5.0	15.5	66.8	5.0	16.0	-
12	N-(2-pyrimidyl)nicotinamide	A	173-175	C ₁₀ H ₈ N ₄ O			28.0			27.8	+
13	2-(Nicotinylamino)-phenol	A	200 dec.	C ₁₂ H ₁₀ N ₂ O ₂	67.3	4.7	13.1	67.3	4.7	13.0	--
14	3-(Nicotinylamino)-phenol	A	215-218	C ₁₂ H ₁₀ N ₂ O ₂	67.3	4.7	13.1	67.7	4.9	13.0	-
15	4-(Nicotinylamino)-phenol	A	203-205	C ₁₂ H ₁₀ N ₂ O ₂	67.3	4.7	13.1	67.0	4.6	13.3	-
16	2-(Nicotinylamino)-5-carbethoxythiazole	A	187-192	C ₁₂ H ₁₁ N ₃ O ₃ S	52.0	4.0	15.2	51.0	4.0	15.7	-
17	N-propylnicotinamide		89- 92	C ₉ H ₁₂ N ₂ O	65.9	7.3	17.1	65.9	7.2	16.8	C
18	N-isopropylnicotinamide		85- 86.5	C ₉ H ₁₂ N ₂ O	65.9	7.3	17.1	66.0	7.6	17.1	+
19	N-methoxypropylnicotinamide	B		C ₁₀ H ₁₄ N ₂ O ₂			14.4			14.0	-
20	N-butylnicotinamide		34- 37	C ₁₀ H ₁₄ N ₂ O	67.4	7.9	15.7	67.4	8.0	15.7	+
21	p-(Nicotinylamino)acetanilide	A	275-278	C ₁₄ H ₁₂ N ₂ O ₂	65.9	5.1	16.5	66.3	5.2	16.9	-
22	6-Chloronicotinamide (5)		212-213	C ₆ H ₄ ClN ₂ O	46.2	3.2	18.0	46.0	3.5	17.6	-
23	6-Aminonicotinamide		243-244	C ₆ H ₇ N ₃ O	52.6	5.1	30.7	52.9	5.3	30.3	-
24	6-Butoxynicotinamide		150-151	C ₁₆ H ₁₈ N ₂ O ₂	61.9	7.2	14.4	61.9	7.1	14.5	-
25	p-(Nicotinylamino)benzoic acid		298-299	C ₁₃ H ₁₀ N ₂ O ₃	64.5	4.1	11.6	64.0	4.6	11.7	-

A. Prepared in approximately the same manner as N-nicotinyl-3-aminopyridine shown in the Experimental.

Compounds 1, 3, 9, and 21 were recrystallized from alcohol.

Compounds 2, 5, and 6 were recrystallized from acetone.

Compounds 10 and 16 were purified by reprecipitation from an acid solution by alkali.

Compound 7 from benzene-petroleum ether.

Compound 12 from chloroform.

Compound 4 from water.

B. Liquid of b.p. 235-240° at 14 mm.

C. Not tested.

The basis of activity is in relationship to that of streptomycin in mice.

Those compounds with + show approximately 25% activity, while ++ is approximately 50% of streptomycin activity.

The compounds were usually fed in a 0.25% synthetic diet. For complete details see the report of D. McKenzie (2).

was added simultaneously 24 g. (0.17 mole) of nicotinyl chloride and a dilute sodium hydroxide solution, so that the reaction mixture was kept slightly alkaline. The product resulting from acidification was washed successively with water and alcohol. The crude product was dissolved in alkali, treated with Norit, and reprecipitated; wt. 15 g., m.p. 298–299°.

N-Propylnicotinamide. A mixture of 7.5 g. (0.05 mole) of ethyl nicotinate and 15 g. (0.26 mole) of *n*-propylamine was heated for 18 hours at 150°. The excess propylamine was removed in a vacuum and the residue crystallized upon trituration with high-boiling petroleum ether; wt. 8 g., m.p. 89–92°.

N-Isopropylnicotinamide. To a mixture of 12.2 g. (0.02 mole) of isopropylamine and 100 g. of cracked ice was added dropwise 10 g. (0.07 mole) of nicotinyl chloride. The reaction mixture was extracted twice with 200 ml. portions of chloroform and the chloroform was boiled off. The solid residue weighed 7.5 g. After recrystallization from chloroform-petroleum ether it melted at 85–86.5°.

N-Methoxypropylnicotinamide. Forty grams (0.45 mole) of methoxypropylamine and 15.2 g. (1.07 mole) of nicotinyl chloride synthesized in the same manner as the isopropyl analog gave 10 g. of the desired product as a light yellow oil, b.p. 235–240° (14 mm.).

N-Butylnicotinamide. Two and one-half grams of the desired product was obtained using the same procedure with 3 g. (0.04 mole) of *n*-butylamine and 3 g. (0.02 mole) of nicotinyl chloride. The product obtained from the removal of chloroform could be crystallized by cooling in a dry-ice bath and scratching. The product after trituration with low-boiling petroleum ether and a few drops of chloroform was filtered. The compound melted on the microstage at 34–37° w.p.s. It did not lend itself to successful recrystallization.

Methyl coumalate. Coumalic acid was prepared according to the directions of von Pechmann (4). We found it more desirable to form the methyl ester by adding an ethereal solution of diazomethane to an alcohol suspension of the acid than by the vigorous esterification procedure used by von Pechmann.

6-Chloronicotinamide (5). A mixture of 100 g. (0.5 mole) of phosphorus pentachloride, 100 g. (0.67 mole) of phosphorus oxychloride, and 50 g. (0.36 mole) of 6-hydroxynicotinamide (4) (prepared from methyl coumalate and ammonia) was cautiously added to 600 ml. of ice-cold concentrated ammonium hydroxide and 400 ml. of water. The crude washed product weighed 32 g., m.p. 203–205°, and after recrystallization from alcohol it melted at 212–213°.

6-Aminonicotinamide. A mixture of 5 g. (0.03 mole) of 6-chloronicotinamide and 50 ml. of concentrated ammonium hydroxide was heated for 6–8 hours at 170° in a bomb. The crude product weighed 2.5 g.; it melted at 257–260° after recrystallization from water. The ammoniacal filtrate deposited approximately 1 g. of 6-hydroxynicotinic acid upon acidification. Marckwald (6) reports m.p. 243–244°.

6-Butoxynicotinamide. A mixture of 5 g. (0.03 mole) of 6-chloronicotinamide and 3.5 g. (0.04 mole) of sodium butoxide in 25 ml. of butanol was refluxed for thirty minutes on a steam cone. The cooled reaction mixture was filtered and washed with water, wt. 2.5 g. After three recrystallizations from alcohol it melted at 150–151°.

SUMMARY

A series of 25 substituted nicotinamides have been synthesized and tested for tuberculostatic activity. The most active compound prepared N-(2-thiazolyl)-nicotinamide is less active than nicotinamide as a tuberculostatic agent.

PEARL RIVER, N. Y.

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7-DEHYDROCHOLESTERYL CHLORIDE AND BROMIDE

SEYMOUR BERNSTEIN, KARL J. SAX, AND Y. SUBBAROW

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The purpose of this paper is to describe the preparation of 7-dehydrocholesteryl chloride (III) and bromide (IX) hitherto unreported in the literature. The preparation of these compounds directly from 7-dehydrocholesterol with halogenating agents appeared unpromising in view of previous work on ergosterol. Rygh (1) found that treatment of ergosterol with phosphorus oxychloride gave as the chief product ergostatetraene A along with a small amount of ergosteryl phosphate but none of the desired ergosteryl chloride. Consequently, it was not surprising that our attempts to prepare the desired halides from 7-dehydrocholesterol with thionyl chloride, oxalyl chloride, phosphorus oxychloride, and phosphorus tribromide were unsuccessful.

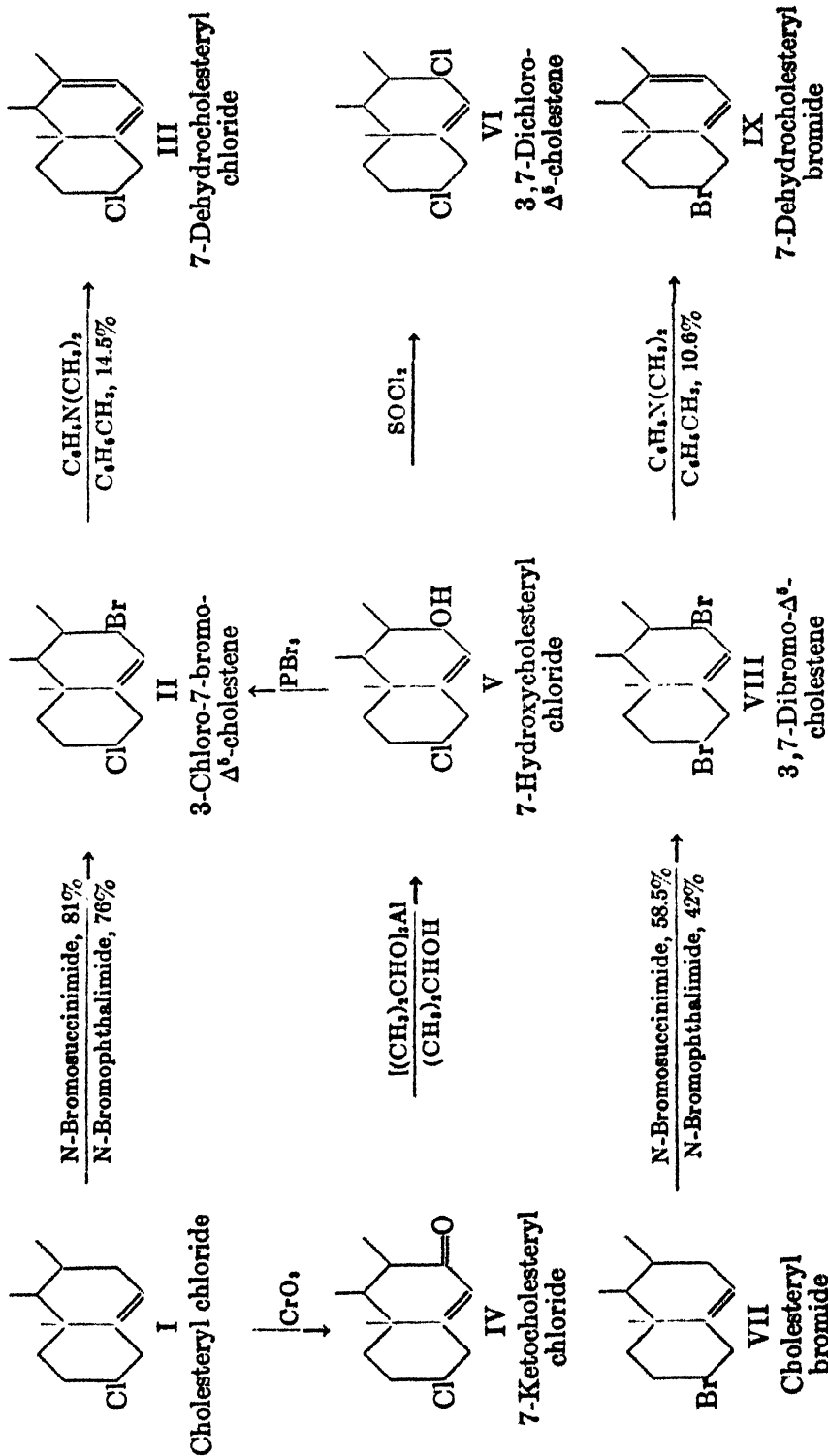
However, it has been found that 7-dehydrocholesteryl chloride and bromide may be prepared from cholesteryl chloride (I)¹ and bromide (VII) resp. Cholesteryl chloride was brominated in carbon tetrachloride with N-bromosuccinimide according to the method of Ziegler (2) to give in 81% yield 3-chloro-7-bromo- Δ^5 -cholestene (II). A 76% yield was obtained with N-bromophthalimide. 3-Chloro-7-bromo- Δ^5 -cholestene was selectively dehydrohalogenated by being refluxed with dimethylaniline in toluene to give the desired 7-dehydrocholesteryl chloride in 14.5% yield. Similarly, cholesteryl bromide was converted to 3,7-dibromo- Δ^5 -cholestene (VIII) in 58.5% yield with N-bromosuccinimide, and in 42% yield with N-bromophthalimide; the dibromo compound on treatment with dimethylaniline in toluene gave a 10.6% yield (crude) of 7-dehydrocholesteryl bromide (IX).

The postulated structures of the intermediate 7-bromo compounds were substantiated in the following manner. 7-Hydroxycholesteryl chloride (V) prepared according to Marker and co-workers (3) (I \rightarrow IV \rightarrow V) was treated with phosphorus tribromide to give 3-chloro-7-bromo- Δ^5 -cholestene identical in melting point and optical rotation with the product obtained by direct bromination of cholesteryl chloride. It is apparent that introduction of bromine in the C-7 position creates a new asymmetric center; thus two diastereomeric bromo compounds are possible. They may be designated as *e.g.* 3-chloro-7(α)-bromo- Δ^5 -cholestene and 3-chloro-7(β)-bromo- Δ^5 -cholestene. However, in the work being presented here we prefer not to specify such configurations.

As an incidental experiment, 7-hydroxycholesteryl chloride was converted to 3,7-dichloro- Δ^5 -cholestene (VI) with thionyl chloride.

The postulated structures of the 7-dehydrocholesteryl chloride and bromide may be supported by the following arguments: (A) analyses show the presence of only one atom of halogen; (B) the method of synthesis is based on the estab-

¹ Shoppee, *J. Chem. Soc.*, 1138, 1147 (1946), has presented evidence which shows that cholesteryl chloride is actually 3(β)-chloro- Δ^5 -cholestene.



lished structure of the intermediate 7-bromo compound; (C) the high negative rotations of 7-dehydrocholesteryl chloride and bromide are in conformity with the

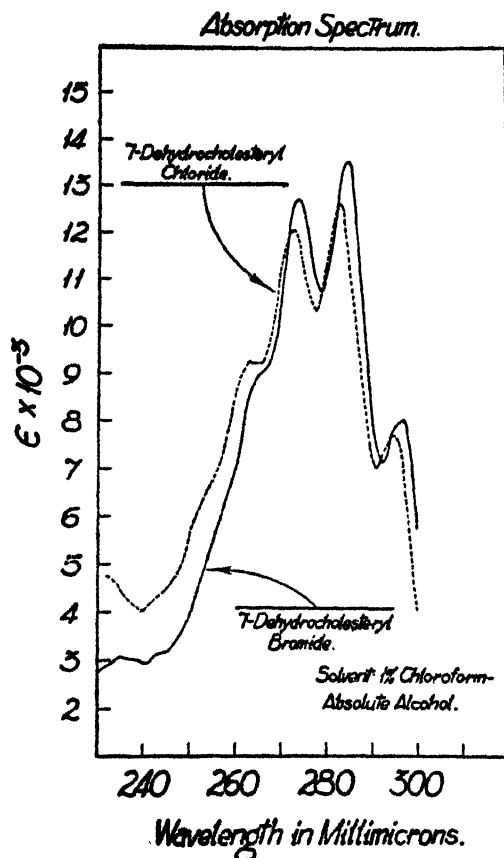


FIG. 1

TABLE I
PHYSICAL PROPERTIES

COMPOUNDS	M.P., °C.	$[\alpha]_D$ (CHCl ₃)	ULTRAVIOLET ABSORPTION SPECTRUM MAXIMA,* mμ
3-Chloro-7-bromo- Δ^5 -cholestene.....	136-138 d.	-223°	—
3,7-Dichloro- Δ^5 -cholestene.....	117-119	-165°	—
3,7-Dibromo- Δ^5 -cholestene.....	142.5-144.5	-198.4°	None
7-Dehydrocholesteryl chloride.....	130-132	-91.1°	263, 273, 283 and 295
7-Dehydrocholesteryl bromide.....	142-144	-78.7°	235, 274, 285 and 297

* Solvent: 1% chloroform-absolute alcohol, the substance was dissolved in 1 ml. of chloroform and rapidly diluted to 100 ml. with absolute alcohol.

optical rotation theory of 7-dehydrosterols (4); and (D) the two compounds have the qualitatively characteristic ultraviolet absorption spectrum (Figure 1) of 7-dehydrosterols, such as ergosterol and 7-dehydrocholesterol (5). Conversion

of the 7-dehydrocholesteryl halides to 7-dehydrocholesterol or its acetate would chemically corroborate the structures. This, unfortunately, has not been accomplished under a variety of conditions. In this connection it is interesting to note that 7-dehydrocholesteryl chloride was recovered unchanged when refluxed with silver acetate in benzene for 16 hours, and when shaken with silver acetate or silver oxide in ether for 64 hours.

In Table I there are listed the physical properties of the five new halogenated sterols herein presented.

In light of subsequent experience with bromination of steroids with N-bromosuccinimide, it is believed that our yields may be open for improvement. The yields in the bromination reaction may be improved by using more than one equivalent of the brominating agent, and, in the selective dehydrohalogenation reaction, by refluxing with another stripping agent such as γ -collidine in xylene for as short a time as 15–20 minutes.

An investigation of the ultraviolet irradiation of 7-dehydrocholesteryl chloride and bromide to give possibly Vitamin D₂ chloride and bromide has been set aside for future work.

EXPERIMENTAL

3-Chloro-7-bromo- Δ^5 -cholestene (II). A. A mixture of 1 g. (0.0025 *M*) of cholesteryl chloride (I), m.p. 94–96°, 0.45 g. (0.0025 *M*) of N-bromosuccinimide, and 25 ml. of carbon tetrachloride was refluxed for 10 minutes, cooled, and the succinimide was removed. The filtrate was evaporated *in vacuo* and this gave a very viscous yellow oil intermixed with solid. The residue was worked with acetone and the resulting white solid was collected, wt. 0.44 g., m.p. 135–140° d. From the mother liquor two additional fractions of product were obtained, 0.09 g., m.p. 131–136° d., and 0.3 g., m.p. 135–137° d. The three fractions were combined and recrystallized three times from acetone, wt. 0.37 g., m.p. 136–138° d. (very slight decomposition at 134–136°), $[\alpha]_D^{25} - 234.4^\circ$, $[\alpha]_D^{25} - 223^\circ$ (12.8 mg., 7.2 mg. in 2 ml. of chloroform, 1 dcm. semi-micro tube, gave $\alpha_D^{25} - 1.50^\circ$, and $\alpha_D^{25} - 0.804^\circ$ resp.).

Anal. Calc'd for C₂₇H₄₄BrCl: C, 67.00; H, 9.16; BrCl, 23.84.

Found: C, 67.31; H, 9.36; BrCl, 24.00.

In another run with 24.27 g. (0.06 *M*) of cholesteryl chloride (I), 10.8 g. (0.06 *M*) of N-bromosuccinimide and 250 ml. of carbon tetrachloride there was obtained 23.6 g. of pure product, m.p. 136–139° d., 81% yield.

B. A mixture of 4.05 g. (0.01 *M*) of cholesteryl chloride (I), 2.26 g. (0.01 *M*) of N-bromophthalimide and 50 ml. of carbon tetrachloride was refluxed for 10 minutes, cooled, and the phthalimide was removed. The filtrate was evaporated *in vacuo*, and the residue was treated with acetone and was set in the refrigerator overnight. The solid was collected, washed with acetone, wt. 3.68 g., m.p. 134–140° d. (the majority of the material melted at 137–140°), 76% yield. Recrystallization from acetone gave 2.87 g. of product, m.p. 139–142° d.

C. A solution of 0.42 g. of 7-hydroxycholesteryl chloride (V) in 20 ml. of dry benzene was treated in the cold with 0.05 ml. of phosphorus tribromide, and the mixture was allowed to stand at room temperature overnight. Ice-water was added and the benzene extract was washed successively with water, sodium bicarbonate solution and saturated saline, and was dried with magnesium sulfate. The benzene was evaporated *in vacuo* and the residue was dissolved in acetone. This solution was maintained at –6° for 4 days, and the crystals that separated were collected, m.p. 132–136° d. Recrystallization to constant melting point and rotation gave 35 mg., m.p. 137.5–139.5° d., $[\alpha]_D^{25} - 223^\circ$ (7.0 mg. in 2 ml. chloroform, 1 dcm. semi-micro tube, gave $\alpha_D^{25} - 0.78^\circ$). A mixed melting point determina-

tion with the material prepared above, preparation A, showed no depression, m.p. 138–140° d.

3,7-Dichloro- Δ^5 -cholestene (VI). A solution of 0.42 g. of 7-hydroxycholesteryl chloride (V) in 20 ml. of dry benzene was treated cold with 0.25 ml. of thionyl chloride, and the mixture was allowed to stand at room temperature overnight. The solvent and excess thionyl chloride were removed *in vacuo* and the residue was recrystallized four times from acetone, wt. 25 mg., m.p. 117–119°, $[\alpha]_D^{25} -165^\circ$ (7.45 mg. in 2 ml. of chloroform, 1 cm. semi-micro tube, gave $\alpha_D^{25} -0.62^\circ$).

Anal. Calc'd for $C_{27}H_{44}Cl_2$: C, 73.78; H, 10.09; Cl, 16.13.

Found: C, 74.18; H, 10.10; Cl, 15.76.

3,7-Dibromo- Δ^5 -cholestene (VIII). A. A mixture of 2.45 g. (0.0055 *M*) of cholesteryl bromide (VII), m.p. 96–98.5°, 0.99 g. (0.0055 *M*) of *N*-bromosuccinimide, and 50 ml. of carbon tetrachloride was refluxed on the steam-bath for one hour, cooled, and the succinimide was removed. The filtrate was evaporated *in vacuo* and a viscous yellow-brown oil was obtained. The oil was worked with acetone giving crystals, wt. 1.26 g., m.p. 130–135.5° d. Four recrystallizations from acetone to constant melting point gave 0.33 g., m.p. 142.5–144.5° d., $[\alpha]_D^{25} -198.4^\circ$ (12.5 mg. in 2 ml. of chloroform, 1 cm. semi-micro tube gave $\alpha_D^{25} -1.24^\circ$). Additional amounts of the product can be obtained from the mother liquors. The product showed no absorption maxima in the ultraviolet.

Anal. Calc'd for $C_{27}H_{44}Br_2$: C, 61.36; H, 8.38; Br, 30.25.

Found: C, 61.69; H, 8.67; Br, 30.60.

In another run, a mixture of 8.98 g. (0.02 *M*) of cholesteryl bromide (VII), 3.6 g. (0.02 *M*) of *N*-bromosuccinimide, and 150 ml. of carbon tetrachloride was refluxed on the steam-bath for 12 minutes while being irradiated with an ultraviolet lamp. The product was worked up in the above described manner, 6.2 g., m.p. 137–144° d., 58.5% yield. Recrystallization from ether-acetone gave 4.59 g., m.p. 139–142° d.

B. A mixture of 9.0 g. (0.02 *M*) of cholesteryl bromide (VII), 4.52 g. (0.02 *M*) of *N*-bromophthalimide, and 75 ml. of carbon tetrachloride was refluxed for 20 minutes. The product was worked up in the usual manner, wt. 6.2 g., m.p. 133–140° d. Recrystallization from acetone gave 4.43 g., m.p. 142–145.5° d., 42% yield.

7-Dehydrocholesteryl chloride (III). A mixture of 1 g. of 3-chloro-7-bromo- Δ^5 -cholestene (II), 0.5 ml. of dimethylaniline in 50 ml. of toluene was refluxed in a nitrogen atmosphere for 1.5 hours, cooled, and anhydrous magnesium sulfate was added. The mixture was filtered and the filtrate was evaporated *in vacuo*. This gave an oil, which was treated with alcohol and warmed. A partial solution resulted, ether was added to effect complete solution. The solution was concentrated and cooled and needles separated, wt. 0.17 g., m.p. 119–125°. The product was recrystallized from ether-methanol to constant melting point and ultraviolet absorption, wt. 0.12 g., 14.5% yield, m.p. 130–132°, $[\alpha]_D^{25} -91.1^\circ$ (11.2 mg. in 2 ml. of chloroform, 1 cm. semi-micro tube, gave $\alpha_D^{25} -0.51^\circ$), ultraviolet absorption maxima at 263, 273, 283, and 295 $m\mu$, $\epsilon = 9250, 12070, 12600$, and 7700 resp.

Anal. Calc'd for $C_{27}H_{43}Cl$: C, 80.45; H, 10.75; Cl, 8.80.

Found: C, 79.98; H, 10.73; Cl, 8.67.

7-Dehydrocholesteryl bromide (IX). A mixture of 1 g. of 3,7-dibromo- Δ^5 -cholestene (VIII), 0.5 ml. of dimethylaniline, and 50 ml. of toluene was refluxed in a nitrogen atmosphere for 1.5 hours. The mixture was cooled and filtered after the addition of anhydrous magnesium sulfate. The water-white filtrate was evaporated *in vacuo* and gave an oily residue which was dissolved in ether-alcohol. Concentration and cooling gave an oil which on being worked became partially crystalline, wt. 0.23 g., mixture of white crystals and brown-yellow semi-solid. Two recrystallizations from ether-methanol gave 90 mg., m.p. 139–142.5°, 10.6% yield. A sample was recrystallized to constant melting point from ether-methanol, m.p. 142–144°, $[\alpha]_D^{25} -78.7^\circ$ (15 mg. in 2 ml. chloroform, 1 cm. semi-micro tube gave $\alpha_D^{25} -0.59^\circ$), ultraviolet absorption maxima at 235, 274, 285, and 297 $m\mu$, $\epsilon = 3050, 12710, 13550$, and 8040 resp.

Anal. Calc'd for $C_{27}H_{43}Br$: C, 72.46; H, 9.68; Br, 17.86.

Found: C, 72.77, 72.91; H, 10.39, 9.73; Br, 17.46.

Acknowledgment. We wish to thank Messrs. Louis Brancone, William Fulmor, Samuel Modes, and Oscar Dike for the microanalyses, and also Mr. Leslie H. McWilliams for the drawing of Figure 1.

SUMMARY

7-Dehydrocholesteryl chloride and bromide have been prepared from cholesteryl chloride and bromide resp. with N-bromosuccinimide or N-bromophthalimide with subsequent elimination of hydrogen bromide.

PEARL RIVER, N. Y.

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CONDENSATION OF HYDROXY AND METHOXY N-METHYLBENZYLAMINES WITH HETEROCYCLIC CHLORIDES

NORMAN H. CROMWELL

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It had been found that one of the N-methylbenzylamines, namely, *o*-hydroxy-N-methylbenzylamine, reported in a previous communication (1), showed mild activity against avian malaria (2). It therefore seemed important to attempt to obtain more active antimalarials through a combination of such benzylamino groups with the pharmacologically important groupings, 2-amino-4-pyrimidyl and 7-chloro-4-quinolyl.

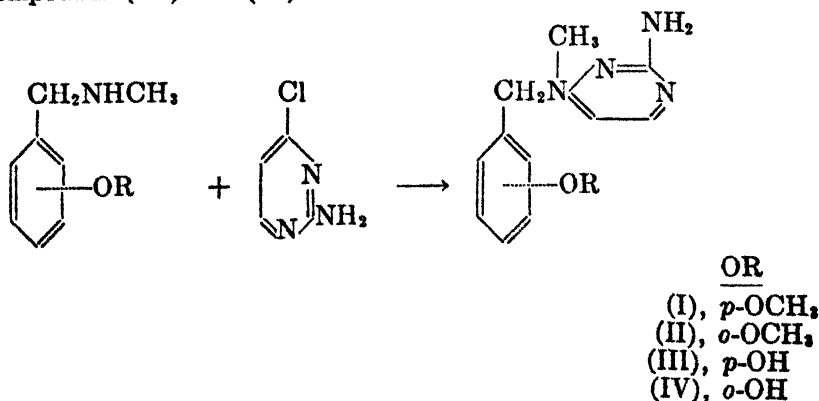
TABLE I
PHYSICAL AND ANALYTICAL DATA

2-AMINO-4-(N'-METHYLBENZYL-AMINO)PYRIMIDINES	NO.	M.P. YIELD		FORMULA	% NITROGEN	
		°C.	%		Calc'd	Found
<i>p</i> -Methoxy	(I)	145	70	C ₁₃ H ₁₆ N ₄ O	22.94	23.15
<i>o</i> -Methoxy	(II)	150	60	C ₁₃ H ₁₆ N ₄ O	22.94	22.98
<i>p</i> -Hydroxy	(III)	213	40	C ₁₂ H ₁₄ N ₄ O	24.33	24.32
<i>o</i> -Hydroxy	(IV)	208	31	C ₁₂ H ₁₄ N ₄ O	24.33	24.38
7-CHLORO-4-(BENZYLAMINO)-QUINOLINES						
N'methyl- <i>p</i> -methoxy . . .	(V)	105-107	20	C ₁₅ H ₁₇ ClN ₂ O ^a		
<i>p</i> -Hydroxy	(VI)	253-255	5	C ₁₆ H ₁₃ ClN ₂ O ^b		

^a Calc'd: C, 63.11; H, 5.48. Found: C, 63.50; H, 5.50.

^b Calc'd: C, 67.48; H, 4.60. Found: C, 67.08; H, 4.95.

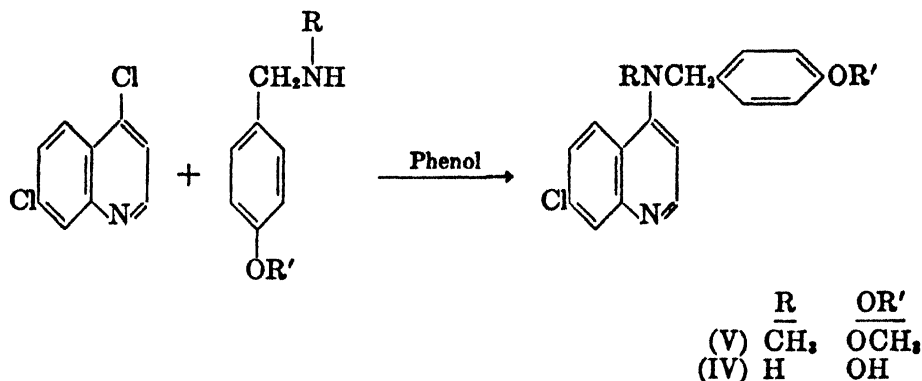
The *p*-methoxy and *o*-methoxy-N-methylbenzylamines reacted with 2-amino-4-chloropyrimidine to give good yields of the expected products (I) and (II), while the corresponding hydroxy-N-methylbenzylamines gave only fair to poor yields of compounds (III) and (IV).



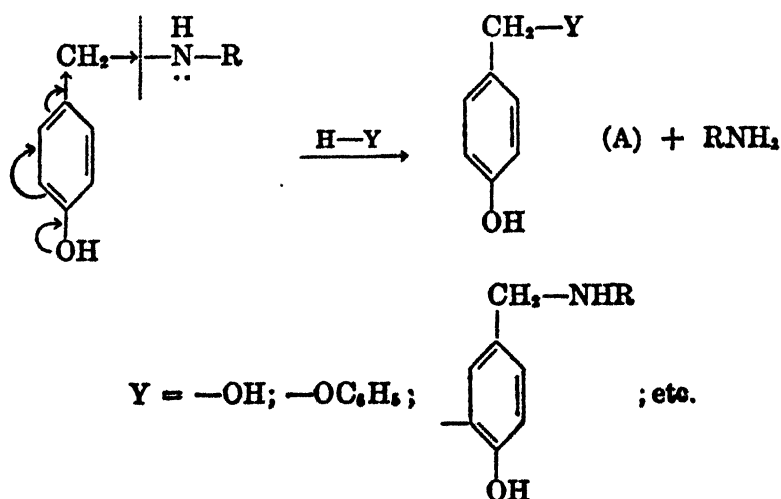
p-Hydroxybenzylamine (3) was too unstable under the conditions required for such condensations to give a product other than a resin.

In some simple experiments designed to check the lability of the benzyl-to-nitrogen bond in these *ortho*- and *para*-hydroxybenzylamines, it was found that ammonia or methylamine is readily lost when water solutions of such compounds are heated for a short time. In the earlier communication it was observed that such decompositions are experienced when these amines are heated alone (1).

4,7-Dichloroquinoline was condensed with *p*-methoxy-*N*-methylbenzylamine to give a low yield of (V) and with *p*-hydroxybenzylamine to give a trace of (VI). Most of the *p*-hydroxybenzylamine decomposed to give off ammonia in this latter reaction. *p*-Hydroxy-*N*-methylbenzylamine formed only resins in such attempted condensations.

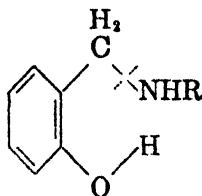


It seems evident that the *ortho*- and *para*-hydroxybenzylamines are not promising compounds for such condensations because of the ease with which they undergo the following types of decomposition,



The products (A) are insoluble resin-like substances probably of the phenol-formaldehyde type, when the *ortho*- and *para*-hydroxybenzylamines undergo

self-condensation. The presence of the hydroxyl group in the *ortho* or *para* position would of course be expected to labilize this benzyl-to-nitrogen bond through a mesomeric (resonance) effect transmitted along the side chain by an inductive effect. The fact that the *ortho*-hydroxy compounds seem to be the more unstable in this respect (1) can probably be ascribed to an additional "ortho" effect operating through chelation to aid in labilizing the benzyl-to-nitrogen bond.



Preliminary studies of the pyrimidines (I), (II), (III) and (IV) showed them to be almost devoid of activity in avian malaria.¹

Acknowledgment. The author appreciates very much a research grant from Parke, Davis and Company of Detroit, Michigan, which aided in the completion of this investigation.

EXPERIMENTAL²

2-Amino-4-(N'methylbenzylamino)pyrimidines

(I) *p*-Methoxy and (II) *o*-Methoxy. The pyrimidines (I) and (II) were prepared by refluxing for three hours mixtures of 8.5 g. (0.057 mole) of *p*-methoxy-N-methylbenzylamine and *o*-methoxy-N-methylbenzylamine (1), respectively with 6.5 g. (0.05 mole) of 2-amino-4-chloropyrimidine in 100 ml. of water and 10 ml. of acetone. After the first thirty minutes of heating, all of the starting materials had dissolved. The solutions were cooled in an ice-bath and made strongly basic with 10% sodium hydroxide. The colorless precipitates were recrystallized twice from alcohol and water.

(III) *p*-Hydroxy and (IV) *o*-Hydroxy. The pyrimidines (III) and (IV) were prepared using the same conditions except that the *p*-hydroxy and *o*-hydroxy-N-methylbenzylamines were introduced as their hydrochlorides (1). To isolate the products the solutions were made strongly basic with conc'd. ammonium hydroxide to give almost colorless precipitates. The pyrimidine (III), 7 g., was recrystallized from 200 ml. of boiling 95% alcohol. It was found it could also be recrystallized from dioxane. This product was quite insoluble in cold benzene, acetone, or absolute alcohol.

Pyrimidine (IV) was insoluble in absolute alcohol, methyl alcohol, benzene, acetone, water-alcohol, chloroform, or chloroform-alcohol. It was recrystallized from boiling isopropyl alcohol (2 g. in 100 ml.) to give pale, salmon-colored needles.

Attempts to condense p-hydroxybenzylamine with 2-amino-4-chloropyrimidine. When the conditions outlined in the above syntheses were applied using the free base, *p*-hydroxybenzylamine (3), only a high-melting resin resulted and ammonia was detected in the hot residual reaction mixture when sodium hydroxide was added. The reaction was repeated under the same conditions, except that the pH of the solution was held between 3.5 and 6

¹ We are indebted to Drs. L. L. Coggeshall and Richard J. Porter of the University of Michigan for the antimalarial testing of these substances.

² Micro-Kjeldahl analyses for nitrogen were determined by the Parke, Davis and Company Research Laboratories, Detroit, Mich.

by an initial addition of hydrochloric acid followed by periodic additions of sodium carbonate solution as the reaction mixture became more acidic on continued heating. The only products isolated were a resin and a small amount of the starting *p*-hydroxybenzylamine.

Heating water solutions of hydroxybenzylamines. One-gram samples of *p*-hydroxybenzylamine, *p*-hydroxy-*N*-methylbenzylamine, and *o*-hydroxy-*N*-methylbenzylamine were boiled for five minutes in dilute hydrochloric acid, the solutions made basic with sodium bicarbonate and boiled for an additional five minutes. In all three cases the odor of ammonia or methylamine was detected during the latter operation. Distillation gave clear distillates from which ammonium chloride and methylamine hydrochloride, respectively, were isolated after neutralization with hydrochloric acid and evaporation. When a water solution of *p*-hydroxybenzylamine was boiled for five minutes the solution became cloudy and ammonia was evolved.

Condensation of 4, 7-Dichloroquinoline with Benzylamines

(a) *With p-methoxy-N-methylbenzylamine.* A mixture of 4.5 g. of *p*-methoxy-*N*-methylbenzylamine, 6.34 g. of 4,7-dichloroquinoline, and 40 g. of phenol was heated at 100° for four hours. The cooled mixture was poured into 600 ml. of water containing 17 g. of sodium hydroxide. The precipitated thick oil was extracted with ether and the ether layer washed with water, dried, and evaporated. Addition of low-boiling petroleum ether followed by cooling caused slow formation of colorless crystals which were recrystallized from 90% alcohol to give (V).

Longer heating for fifteen hours using the above quantities gave about the same yield of (V). Attempts to carry out the condensation in absolute alcohol at pH 3.5 to 6 gave none of (V); most of the 4,7-dichloroquinoline was recovered unchanged.

(b) *With p-hydroxy-N-methylbenzylamine hydrochloride.* Attempted condensations with this amine hydrochloride in water and acetone, in pyridine, in *n*-propyl alcohol, or ethyl alcohol and water gave only resin-like products and unchanged 4,7-dichloroquinoline.

(c) *With p-hydroxybenzylamine.* A mixture of 12.3 g. of *p*-hydroxybenzylamine, 19.3 g. of 4,7-dichloroquinoline, and 50 g. of phenol was heated at 100° for four hours. A colorless solid appeared in the solution at the end of the first hour. The reaction mixture was cooled and 150 ml. of dry acetone and 70 ml. of dry ether added, and 6.0 g. of a white solid was filtered from the mixture. Ninety per cent of this was proved to be ammonium chloride. The residual phenol-ether-acetone solution was treated with an absolute alcohol solution of hydrogen chloride to give 6.4 g. of mixed amine hydrochlorides. This product was dissolved in water and neutralized with sodium bicarbonate to give a small amount of a gray material which after two recrystallizations from a mixture of absolute alcohol, benzene, and petroleum ether gave light gray crystals of (VI).

SUMMARY

1. *p*-Methoxy, *o*-methoxy, *o*-hydroxy, and *p*-hydroxy-*N*-methylbenzylamines have been condensed with 2-amino-4-chloropyrimidine to give the corresponding 2-amino-4-(*N'*-methylbenzylamino)pyrimidines.

2. *p*-Methoxy-*N*-methylbenzylamine was condensed with 4,7-dichloroquinoline to give 4-(*N'*-methyl-*p*-methoxybenzylamino)-7-chloroquinoline.

3. *p*-Hydroxybenzylamine could not be condensed with 2-amino-4-chloropyrimidine and only low yields resulted from its reaction with 4,7-dichloroquinoline. No identifiable product could be isolated from an attempted condensation of *p*-hydroxy-*N*-methylbenzylamine with this latter heterocyclic chloride.

4. The low yields obtained in certain of these condensations have been shown

to be the result of the lability of the benzyl-to-nitrogen bond in these *ortho* and *para* substituted benzylamines.

LINCOLN, NEBRASKA

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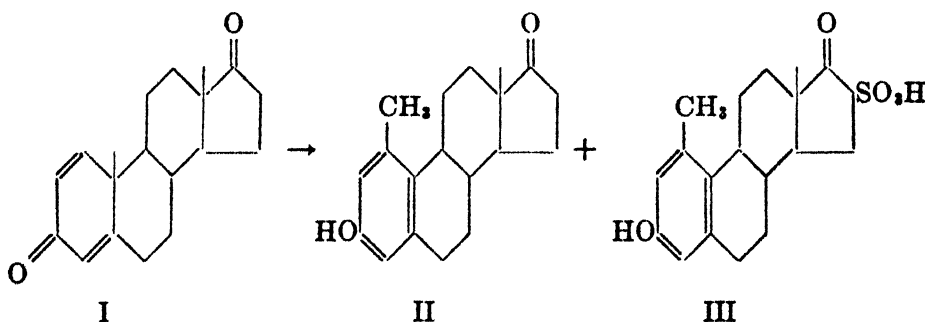
THE SULFONATION OF SOME POLYCYCLIC KETONES

CARL DJERASSI

Received June 14, 1948

Several years ago Windaus and co-workers (1, 2) showed that saturated 3-keto steroids such as cholestan-3-one and coprostan-3-one were converted to the corresponding β -keto sulfonic acids when treated with equimolar quantities of sulfuric acid in acetic anhydride solution at room temperature or below. The conditions for the sulfonation, therefore, are identical with those employed for dienone-phenol rearrangements except that in the latter case catalytic amounts of sulfuric acid appear to be sufficient.

In a recent synthesis (3) of 1-methylestrone (II) from 1,4-androstadiene-3,17-dione (I) by a dienone-phenol rearrangement in acetic anhydride-sulfuric acid solution, it was noted that the yield of 1-methylestrone (II) dropped markedly with increasing amounts of sulfuric acid, a water-soluble derivative being formed, and that the latter was nearly the sole product when equimolar quantities of sulfuric acid were used. As reviewed in that paper (3), a considerable number of steroid dienones have been rearranged previously to the isomeric phenols, the yield being more or less independent of the amount of sulfuric acid employed. These dienones differed from I only in that the C-17 carbonyl group was replaced by hydroxyl, carbomethoxyl, or hydrocarbon substituents. It was reasonable to assume, therefore, that in the rearrangement of the dienone (I) sulfonation had occurred to form the β -keto sulfonic acid (III).¹ This observation led to the present study of sulfonic acid derivatives of some 17-keto steroids and related compounds.



With few exceptions, β -keto sulfonic acids do not appear to have been studied (4) and it was of interest to examine some of their properties, particularly in view

¹ Windaus (1, 2) also showed that α,β -unsaturated ketones such as Δ^4 -cholesten-3-one could be sulfonated in the 6 position under those conditions and it might be suggested, therefore, that the by-product obtained in the rearrangement of I is due to sulfonation at C-6. If that were true, the same relation between yield and amount of sulfuric acid should have been observed in all the other steroid dienones reviewed in the preceding paper (3), which was not the case.

of their formal resemblance to β -keto acids. As a model ketone, 1-keto-1,2,3,4-tetrahydrophenanthrene (IV) was chosen, since it represented a fairly readily available starting material from which crystalline derivatives could be expected. Furthermore, it resembled the 17-keto steroids to be discussed below in that only one adjacent methylene position was unsubstituted. Some analogies in the behavior of the corresponding sulfonic acids could thus be expected.

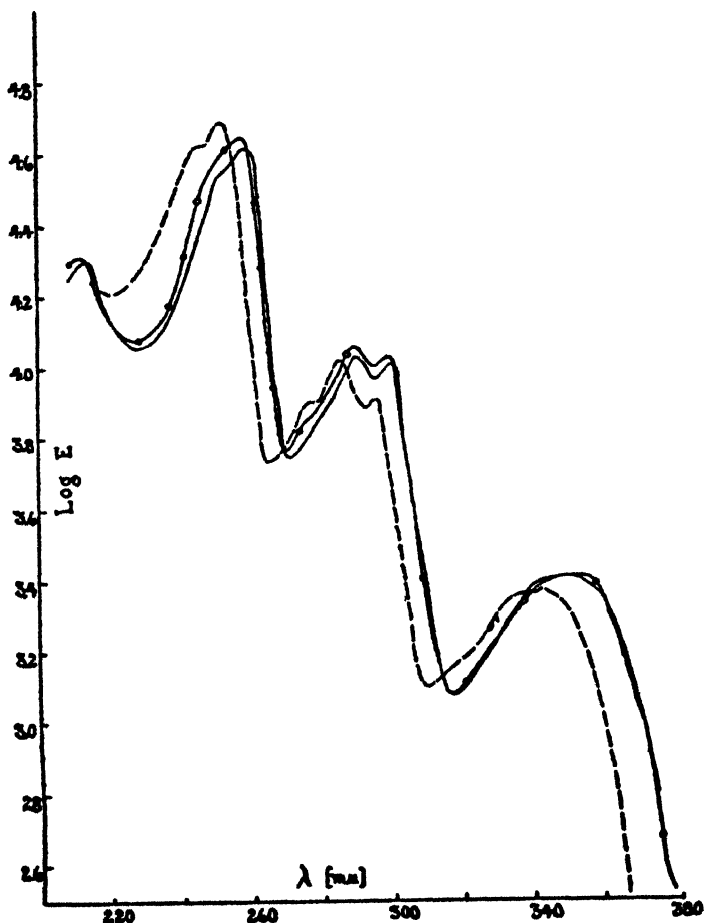


Fig. 1. Ultraviolet absorption spectra (in 95% ethanol solution: --- 1-ketotetrahydrophenanthrene (IV); $\bigcirc\bigcirc\bigcirc$ methyl 1-ketotetrahydrophenanthrene-2-sulfonate (Vb); — methyl 1-keto-2-methyltetrahydrophenanthrene-2-sulfonate (VIIIb)).

When the ketone IV in acetic anhydride solution was allowed to stand at room temperature for two hours with an equimolar amount of concentrated sulfuric acid, there was obtained in high yield a crystalline, water-soluble sulfonic acid, which could be recovered unchanged on boiling for three hours with dilute hydrochloric acid, thus excluding the possible formation of an enol sulfate. Only two structures remain for consideration, namely an aromatic sulfonic acid (improbable because of the mild reaction conditions) or the β -keto sulfonic acid (Va).

The acid reacted instantaneously with diazomethane to yield a methyl ester, which was soluble in cold 5% sodium hydroxide solution and could be recovered unchanged on acidification. This definitely proved the structure Va for the acid and Vb for the methyl ester. A similar acidity has been demonstrated in certain disulfones (5) and is of course to be expected by analogy to β -keto esters. Attempts to prepare ketone derivatives of the methyl ester failed. For instance,

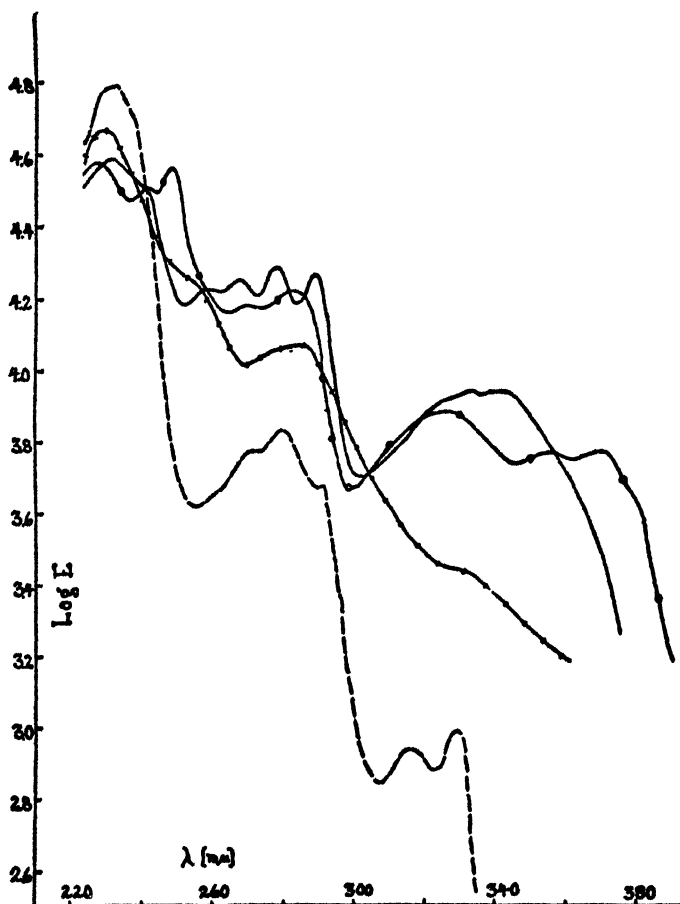
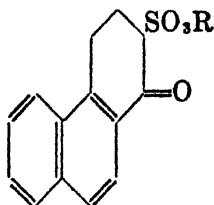
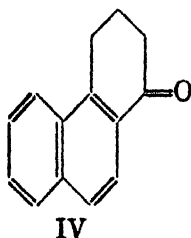


FIG. 2. Ultraviolet absorption spectra (in 5% sodium hydroxide solution): — methyl 1-ketotetrahydrophenanthrene-2-sulfonate (fresh solution); - - - same after standing for four weeks; \bigcirc - \bigcirc - \bigcirc 1-phenanthrol; β -naphthoic acid.

when Vb was treated with dinitrophenylhydrazine, the dinitrophenylhydrazine salt Ve was obtained, identical with a sample prepared from the free acid Va. A similar failure to obtain a phenylhydrazone of acetophenone- ω -sulfonic acid has been mentioned (6). It is likely that the phenylhydrazone obtained by Windaus and Kuhr (1) in the case of cholestanone-2-sulfonic acid actually represented the phenylhydrazine salt of the ketone sulfonic acid. The ultraviolet absorption spectrum (Fig. 1) of the methyl ester Vb in ethanol,

except for a slight bathochromic shift, closely resembles that of the parent ketone IV (7), which would indicate that the compound exists predominantly in the keto form. When measured in sodium hydroxide solution (Fig. 2), the main maximum at 257 m μ due to the carbonyl group in conjugation with the aromatic nucleus (7) disappeared, and the spectrum resembled that of 1-phenanthrol taken in sodium hydroxide solution. On prolonged standing, the absorption of the sodium hydroxide solution of Vb changed somewhat, possibly due to ring opening to VI; for comparison with the latter, the ultraviolet absorption spectrum of β -naphthoic acid in sodium hydroxide solution is also reproduced.



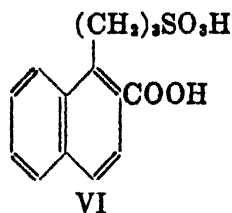
Va R = H

Vb R = CH₃

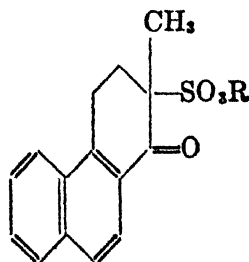
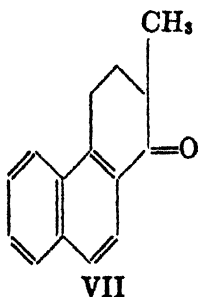
Vc R = H·C₆H₅N

Vd R = H·NH₂

Ve R = H·2,4-(NO₂)₂C₆H₃NHNH₂



Attempts to prepare the 2-methyl derivative VIIIb by alkylating the methyl ester Vb with sodium methoxide and methyl iodide failed, possibly due to cleavage to VI, since β -keto sulfonic acids appear to be labile towards alkali (*cf.* 8, 9). The desired compound could be prepared, however, by sulfonation of 1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene (VII), thus demonstrating that only one free hydrogen atom adjacent to a carbonyl group is necessary for sulfonation under those conditions. In conformance with the assigned structure, the methyl ester VIIIb was insoluble in aqueous alkali and its spectrum in ethanol solution (Fig. 1) was identical with that of Vb.



VIIIa R = H

VIIIb R = CH₃

VIIIc R = H·C₆H₅N

Dehydrogenation of the methyl ester Vb with a palladium catalyst in *p*-cymene solution as a possible route to phenolic sulfonic acids was unsuccessful, since the only pure products were 1-phenanthrol and the ketone IV. A some-

what similar hydrogenolysis has been observed with 1-keto-2-hydroxymethylene-1,2,3,4-tetrahydrophenanthrene (10).

The sulfonation procedure was next applied to some 17-keto steroids in order to prepare the corresponding 16-sulfonic acid derivatives, which have not been described hitherto. Isoandrosterone acetate (IX) and its C-3 epimer, androsterone acetate, readily yielded the corresponding sulfonic acid, which in the case of

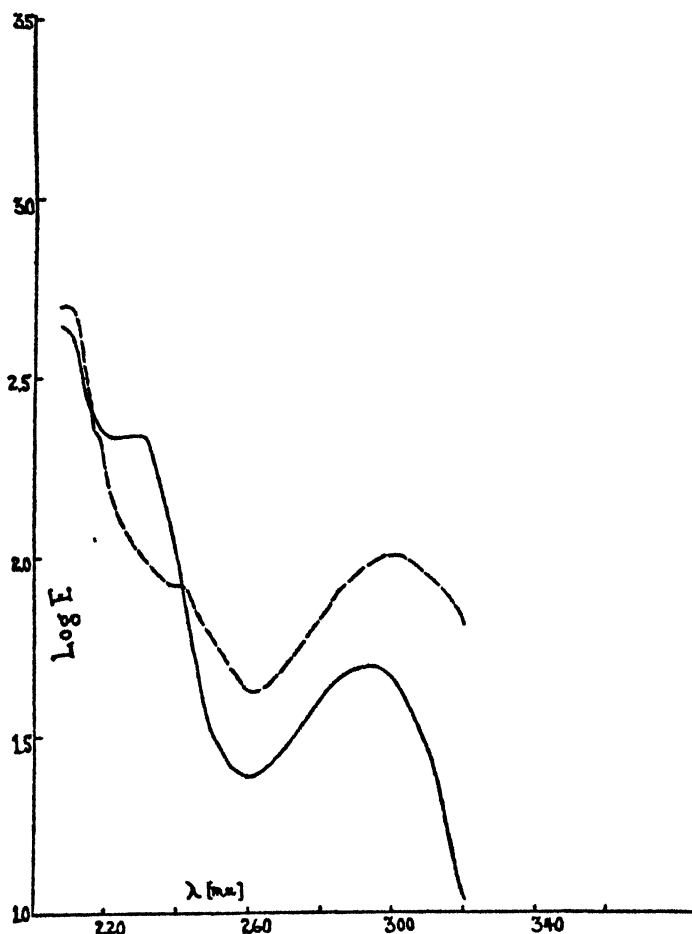
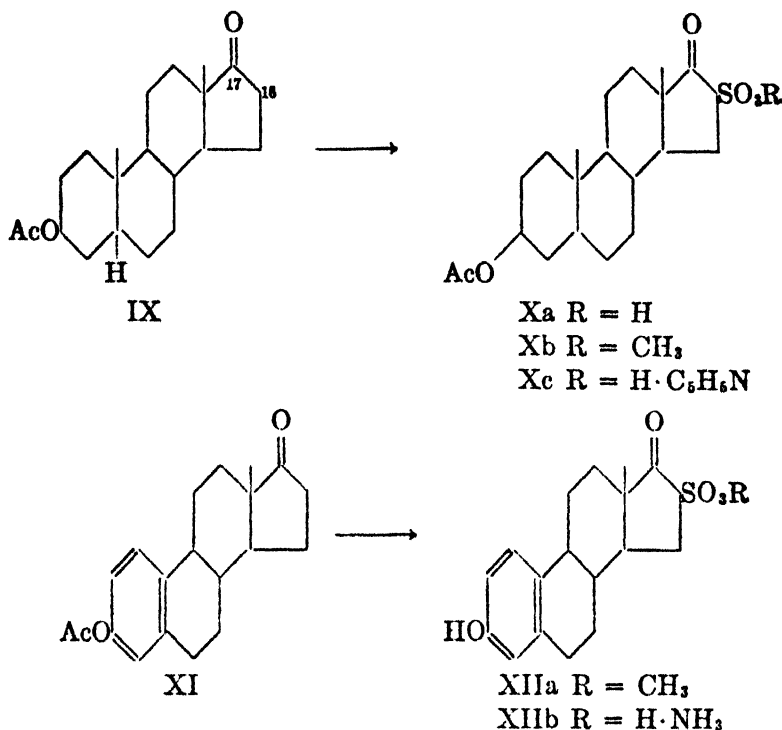


FIG. 3. Ultraviolet absorption spectra (in 95% ethanol solution): — isoandrosterone acetate (IX); --- isoandrosterone acetate 16-sulfonic acid (Xa).

the former could be obtained in crystalline form and which was converted to several derivatives. In this instance also, the ultraviolet absorption spectrum of the sulfonic acid Xa closely resembled that of the parent ketone IX (Fig. 3). It was of particular interest to attempt the sulfonation of estrone acetate (XI), since two derivatives, estrone sulfate and estrone-2 (or 4)-sulfonic acid have already been prepared by Butenandt and Hofstetter (11) by means of chlorosulfonic acid. When the sulfonation was carried out with sulfuric acid in acetic anhydride solution followed by methylation, it was possible to isolate the crys-

talline methyl ester XIIa of estrone-16-sulfonic acid * and thence the ammonium salt XIIb.



Through the courtesy of Dr. Konrad Dobriner, Sloan-Kettering Institute for Cancer Research, New York, and Dr. R. Norman Jones, National Research Council, Ottawa, the infrared absorption spectra of all of the sulfonic acid methyl esters described in this paper have been determined in nujol mulls. The details will be published elsewhere by them, but it is pertinent to mention at this time that all of the compounds showed a strong carbonyl band which was shifted slightly to lower wave length, probably due to the adjacent sulfonic acid group. These data further confirm that the compounds seem to exist in the keto form as indicated already from the ultraviolet absorption spectra.

After it had been demonstrated that sulfonation in the 16-position of 17-keto steroids was achieved readily under conditions prevailing in the dienone-phenol rearrangement, attention was directed towards the isolation of the sulfonation product in the rearrangement of 1,4-androstadiene-3,17-dione (I) mentioned in the second paragraph of this discussion. When one mole of sulfuric acid was employed in the rearrangement of I, almost the entire product was water-soluble and on evaporation afforded an amorphous sulfonic acid, which showed the typical ultraviolet absorption spectrum of a phenol, and thus must be 1-methylestrone-16-sulfonic acid (III) rather than the 16-sulfonic acid derivative

* Nuclear sulfonation was excluded, since estradiol could be recovered as the diacetate under those conditions.

of the starting material I. An analytically pure, though amorphous methyl ester and pyridinium salt were also prepared. It is interesting to note that steroid sulfonic acids such as isoandrosterone acetate 16-sulfonic acid (Xa) or 1-methylestrone-16-sulfonic acid (III) proved to be excellent catalysts in the dienone-phenol rearrangement of 1,4-androstadiene-3,17-dione, and afforded 70–80% of 1-methylestrone (II).

The author is grateful to the Misses Helen Dudek and Jean Rogers for assistance in the experimental work and to Miss Elizabeth Ryan for the ultra-violet absorption spectra.

EXPERIMENTAL³

Sulfonation of 1-keto-1,2,3,4-tetrahydrophenanthrene (IV). A solution of 3.9 g. of the ketone IV in 40 cc. of acetic anhydride was treated dropwise with swirling in an ice-bath with a solution of 2.0 g. of concentrated sulfuric acid in 7 cc. of acetic anhydride and was then allowed to stand at room temperature for two hours. Water was added to hydrolyze the acetic anhydride and the clear solution was evaporated to dryness under reduced pressure, water was added, and the process repeated. The crystalline, very light tan colored residue was triturated with ether-acetone, filtered, and dried in a vacuum desiccator. The yield of 1-ketotetrahydrophenanthrene-2-sulfonic acid hydrate (Va) was 4.96 g. (85%), with the following melting point behavior, unchanged on recrystallization from acetone: partly melting at 154°, solidifying at 158°, darkening at 187°, and decomposing at 194–195°. The acid was recovered unchanged after refluxing for three hours in 5% hydrochloric acid solution. It formed a water-insoluble barium salt.

Anal. Calc'd for $C_{18}H_{14}O_4S \cdot H_2O$: C, 57.13; H, 4.79; S, 10.89; neut. equivalent, 294.

Found: C, 56.80; H, 4.87; S, 10.85; neut. equivalent, 288.

Instantaneous nitrogen evolution was observed when a solution of 2.5 g. of the above sulfonic acid in methanol was treated with excess ethereal diazomethane. After two minutes, the solution was evaporated to dryness, yielding 2.32 g. (94%) of colorless crystals of methyl 1-keto-1,2,3,4-tetrahydrophenanthrene-2-sulfonate (Vb) melting at 101–105°. The analytical sample was recrystallized from ether, and melted at 104–106°. The compound gave no color with alcoholic ferric chloride solution. It was readily soluble in 5% sodium hydroxide solution and was recovered unchanged on acidification. The ultraviolet absorption spectra in 95% ethanol and in 5% sodium hydroxide solution are reproduced in Figs. 1 and 2.

Anal. Calc'd for $C_{18}H_{14}O_4S$: C, 62.05; H, 4.86; S, 11.04; methoxyl, 10.69.

Found: C, 62.38; H, 5.28; S, 10.75; methoxyl, 10.44.

1-Keto-1,2,3,4-tetrahydrophenanthrene-2-sulfonic acid pyridinium salt (Vc). A solution of 100 mg. of the sulfonic acid Va in 1 cc. of methanol was treated with three drops of pyridine and the solution was diluted with absolute ether. The fluffy, colorless needles of the pyridinium salt were filtered, washed well with ether, and dried in a vacuum desiccator; yield, 110 mg., m.p. 199–201°. It gave no color with 5% sodium hydroxide solution.

Anal. Calc'd for $C_{18}H_{17}NO_4S$: N, 3.94; S, 9.02.

Found: N, 3.75; S, 9.45.

1-Keto-1,2,3,4-tetrahydrophenanthrene-2-sulfonic acid ammonium salt (Vd). A solution of 100 mg. of the sulfonic acid Va in 3 cc. of water was treated with one drop of concentrated ammonium hydroxide and the solution was evaporated to dryness. Recrystallization from

³ All melting points are corrected unless noted otherwise. The specific rotations were determined on 5–10 mg. of sample in a 1 dm. tube of 1 cc. capacity. All microanalyses were carried out by Mr. Joseph Alicino, Metuchen, New Jersey and Mr. George L. Stragand, Microchemical Laboratory, University of Pittsburgh.

methanol gave colorless, glistening plates melting at 268° (dec. uncorr.) with softening at about 260°. The same product was obtained when 200 mg. of the methyl ester Vb was heated on the steam-bath with 10 cc. of ammonium hydroxide solution and evaporated to dryness.

Anal. Calc'd for $C_{14}H_{18}NO_4S$: C, 57.32; H, 5.15; N, 4.78; S, 10.93.

Found: C, 57.92; H, 5.56; N, 4.65; S, 11.18.

1-Keto-1,2,3,4-tetrahydrophenanthrene-2-sulfonic acid 2,4-dinitrophenylhydrazinium salt (Ve). To a warm solution of 100 mg. of 2,4-dinitrophenylhydrazine in 5 cc. of ethanol and 0.2 cc. of concentrated hydrochloric acid was added 50 mg. of the methyl ester Vb in an attempt to prepare the phenylhydrazone. After heating for two minutes, a precipitate appeared, whereupon the solution was cooled and the light yellow crystals were filtered and washed; yield, 40 mg., m.p. 213–215° (dec.); found: methoxyl, 0.00. The dinitrophenylhydrazine salt thus produced gave no depression in melting point on admixture with a sample (m.p. 215–216° dec.) prepared by crystallizing equimolar quantities of sulfonic acid Va and dinitrophenylhydrazine from ethanol.

Anal. Calc'd for $C_{20}H_{18}N_4O_6S$: C, 50.63; H, 3.82; N, 11.81; S, 6.74.

Found: C, 50.27; H, 3.87; N, 11.51; S, 6.99.

When a mixture of 70 mg. of the above salt Ve was shaken at room temperature overnight with a few cc. of water and 7 drops of acetone, filtration gave 30 mg. (85%) of acetone dinitrophenylhydrazone of m.p. 124–125°.

Dehydrogenation of methyl 1-keto-1,2,3,4-tetrahydrophenanthrene-2-sulfonate. A mixture of 200 mg. of the methyl ester Vb, 40 mg. of 5% palladized charcoal, and 4 cc. of *p*-cymene was refluxed in an atmosphere of nitrogen for twenty hours. The solution was diluted with ether, the catalyst removed by filtration, and the filtrate was extracted four times with 5% sodium hydroxide solution. Acidification of the extracts gave 20 mg. (15%) of 1-phenanthrol of m.p. 151–153° which on admixture with authentic 1-phenanthrol (m.p. 154–155°) melted at 151–154°. From the neutral fraction, after evaporative distillation under reduced pressure, there was obtained 30% of 1-ketotetrahydrophenanthrene (IV).

Sulfonation of 1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene (VII). The sulfonation of VII was carried out exactly as described for the non-methylated derivative IV and afforded 10% of recovered ketone and 71% of *1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene-2-sulfonic acid hydrate*, which started to melt at 108° solidified at 115° and decomposed at 145–147°.

Anal. Calc'd for $C_{14}H_{16}O_4S \cdot H_2O$: S, 10.40; neut. equivalent, 308.

Found: S, 10.26; neut. equivalent, 303.

Methylation with diazomethane and recrystallization from hexane-acetone gave colorless, shiny crystals of the *methyl ester* VIIb melting at 105–106°. The compound was insoluble in 5% sodium hydroxide solution; its absorption spectrum in ethanol solution is shown in Fig. 2.

Anal. Calc'd for $C_{15}H_{18}O_4S$: C, 63.14; H, 5.20; S, 10.53; methoxyl, 10.20.

Found: C, 62.90; H, 5.27; S, 10.93; methoxyl, 10.36.

The *pyridinium salt* VIIc was prepared in the usual manner, and melted at 99–100° (sealed capillary).

Anal. Calc'd for $C_{15}H_{18}NO_4S$: N, 3.79; S, 8.68.

Found: N, 3.57; S, 8.32.

Sulfonation of isoandrosterone acetate (IX). An ice-cold solution of 665 mg. of isoandrosterone acetate (IX) in 3 cc. of acetic anhydride was treated dropwise with a solution of 200 mg. of sulfuric acid in 3 cc. of acetic anhydride. The dark green solution was allowed to stand at room temperature for two hours, at which time crystals of the sulfonic acid had appeared. After cooling in ice for one-half hour, the colorless crystals were filtered on sintered glass, washed with acetic anhydride and ether, and dried in a vacuum desiccator. The *isoandrosterone acetate 16-sulfonic acid* (Xa) thus obtained was dissolved in acetone and precipitated with ether; yield 520 mg. (63%), m.p. 169–172° (dec.), $[\alpha]_D^{25} +33.5^\circ$ (ethanol). The acid was quite soluble in water, but formed an insoluble barium salt. The ultraviolet

absorption spectrum (Fig. 3) was determined in ethanol solution and showed a maximum at 300 $m\mu$, log E 1.99 and a minimum at 261 $m\mu$, log E 1.62.

Anal. Calc'd for $C_{21}H_{32}O_6S$: C, 61.14; H, 7.82; S, 7.77; acetyl, 10.43.

Found: C, 60.72; H, 7.71; S, 7.42; acetyl, 10.01.

The *methyl ester* Xb, prepared by two minutes treatment with diazomethane, crystallized as rosettes of colorless needles from hexane-acetone or from ethanol, m.p. 189–190°, $[\alpha]_D^{25} +53.3^\circ$ (acetone).

Anal. Calc'd for $C_{22}H_{34}O_6S$: C, 61.94; H, 8.03; S, 7.52; methoxyl, 7.28.

Found: C, 62.02; H, 7.64; S, 7.49; methoxyl, 7.08.

The *pyridinium salt* Xc formed colorless glistening crystals with m.p. 246–248° (dec. uncorr.), $[\alpha]_D^{25} +32.3^\circ$ (ethanol).

Anal. Calc'd for $C_{22}H_{32}NO_6S$: N, 2.85; S, 6.52.

Found: N, 3.15; S, 6.38.

Oxidation of isoandrosterone acetate 16-sulfonic acid (Xa). By analogy to the oxidation of cholestanone-2-sulfonic acid (1), 0.4 g. of the above sulfonic acid Xa in 10 cc. of 90% acetic acid was heated for 2 hours at 60° with a solution of 0.38 g. of chromic anhydride in 5 cc. of 90% acetic acid. After diluting with water and shaking with ether, the latter was extracted with sodium hydroxide solution, the basic extracts were acidified and the precipitated acid was extracted with ether. Evaporation of the dried ether solution and recrystallization from a mixture of hexane and acetone gave 0.09 g. (24%) of colorless crystals of 3(β)-acetoxyalloetibilanic acid with m.p. 229–232°, $[\alpha]_D^{25} -10.3^\circ$ (acetone), thus affording further evidence for the 16-position of the sulfonic acid group.

Anal. Calc'd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48; neut. equiv., 190.

Found: C, 66.68; H, 8.60; neut. equiv., 184.

Sulfonation of androsterone acetate. The reaction was carried out as above, except that 10 cc. of acetic anhydride was necessary to dissolve the ketone. The sulfonic acid did not crystallize out and the reaction mixture was therefore diluted with water, evaporated to dryness under reduced pressure (the acetoxy group being hydrolyzed during this treatment) and the residue in methanol solution was treated with ethereal diazomethane. *Methyl androsterone-16-sulfonate* crystallized as colorless needles from methanol with m.p. 176–178°, $[\alpha]_D^{25} +80^\circ$ (acetone).

Anal. Calc'd for $C_{20}H_{30}O_6S$: C, 62.47; H, 8.39; S, 8.34; methoxyl, 8.07.

Found: C, 62.38; H, 8.25; S, 8.55; methoxyl, 7.84; acetyl, 0.00.

Sulfonation of estrone acetate (XI). The sulfonation² was carried out in the usual manner with 624 mg. of estrone acetate, 200 mg. of concentrated sulfuric acid, and 5 cc. of acetic anhydride. After two hours, the solution was diluted with water and evaporated to dryness under reduced pressure, hydrolysis of the acetate group occurring during that treatment. The residue in methanol solution was treated for a few minutes with diazomethane and evaporated. On careful cooling of a hexane-acetone solution of the residue, decanting twice from oily impurities and scratching, there was obtained 400 mg. (55%) of nearly colorless crystals of *methyl estrone-16-sulfonate* (XIa) of m.p. 188–194° (dec.) and an additional 135 mg. (18.5%) from the mother liquors, which melted at 180–185°. Several recrystallizations led to colorless blades with m.p. 199–200° (dec.), $[\alpha]_D^{25} +139^\circ$ (acetone). The ultraviolet absorption spectrum in ethanol showed a maximum at 281 $m\mu$, log E 3.37 and a minimum at 251 $m\mu$, log E 2.92, characteristic for phenols.

Anal. Calc'd for $C_{19}H_{28}O_6S$: C, 62.61; H, 6.64; S, 8.80; methoxyl, 8.51.

Found: C, 62.77; H, 6.77; S, 8.67; methoxyl, 8.06; acetyl, 0.00

In an attempt to prepare the acetate, the above methyl ester was heated under nitrogen with acetic anhydride for two and one-half hours. After the usual work-up, there was obtained a viscous oil, which could not be induced to crystallize. The ultraviolet absorption spectrum showed maxima at 267.5 $m\mu$, log E 3.09 and 275 $m\mu$, log E 3.06, and minima at 251 $m\mu$, log E 2.97 and 272.5 $m\mu$, log E 3.02. Judging from the analytical figures, the oil appears to be contaminated by some acetic anhydride.

Anal. Calc'd for $C_{21}H_{32}O_6S$: S, 7.89; methoxyl, 7.63; acetyl, 10.59.

Found: S, 6.21; methoxyl, 6.23; acetyl, 11.93.

The methyl ester XIIa was converted to the ammonium salt XIIb by heating 50 mg. with 5 cc. of concentrated ammonium hydroxide solution for one hour and evaporating to dryness. The residue was digested with acetone, filtered, and the precipitate was washed well with acetone; yield 40 mg., m.p. (inserted at 260° in sealed capillary) sintering at 270° with decomposition at 320–323° (uncorr.), $[\alpha]_D^{25} +124^\circ$ (ethanol). The ultraviolet absorption spectrum was identical with that of the methyl ester.

Anal. Calc'd for $C_{18}H_{28}NO_6S$: N, 3.81; S, 8.73.

Found: N, 3.93; S, 8.90.

Dienone-phenol rearrangement of 1,4-androstadiene-3,17-dione (I). (a) *With one mole of sulfuric acid.* The dienone-phenol rearrangement was carried out with 285 mg. of the ketone I and 100 mg. of sulfuric acid in the usual manner (3). After dilution with water, ether extraction, and saponification, there was obtained 20 mg. (7%) of 1-methylestrone (II). The aqueous solution was evaporated to dryness under reduced pressure, water was added, the solution again evaporated, and this process repeated several times. The purplish amorphous residue was then dried in a vacuum desiccator for twenty hours and weighed 230 mg. (63%). It melted at 125–138° with previous softening and since its ultraviolet absorption spectrum showed a maximum at 283 $m\mu$, log E 3.69 and a minimum at 246 $m\mu$, log E 3.27, it is considered to be 1-methylestrone-16-sulfonic acid (III).

Anal. Calc'd for $C_{19}H_{28}O_6S$: S, 8.80.

Found: S, 8.63.

Treatment of the above acid with pyridine and precipitation with ether gave an apparently microcrystalline, light tan precipitate of the pyridinium salt melting with decomposition at 150° (previous softening).

Anal. Calc'd for $C_{21}H_{30}NO_6S$: N, 3.16; S, 7.23.

Found: N, 2.97; S, 7.15.

The sulfonic acid reacted immediately with diazomethane to give a colorless, amorphous methyl ester with m.p. 90–104°.

Anal. Calc'd for $C_{20}H_{28}O_6S$: S, 8.47; methoxyl, 8.20.

Found: S, 8.27; methoxyl, 8.51.

(b) *With 1-methylestrone-16-sulfonic acid (III).* To demonstrate that 1-methylestrone-16-sulfonic acid itself could be a catalyst in the rearrangement in (a), 100 mg. of the dienone I in 2.5 cc. of acetic anhydride was treated with 25 mg. of the amorphous sulfonic acid described above for five hours at room temperature. After working up as usual, there was isolated 70 mg. of 1-methylestrone, m.p. 249–251°.

(c) *With isoandrosterone acetate 16-sulfonic acid (Xa).* The reaction was carried out as above, except that 25 mg. of crystalline isoandrosterone acetate 16-sulfonic acid (Xa) was used and the reaction was carried out on the steam-bath. The yield of 1-methylestrone (II) was 80 mg.

SUMMARY

This paper deals with the preparation and properties of β -keto sulfonic acids derived from 1-ketotetrahydrophenanthrene, its 2-methyl derivative, estrone, androsterone, and isoandrosterone acetate. On the basis of the ready sulfonation of the 17-keto steroids at room temperature with sulfuric acid-acetic anhydride, it was shown that the by-product in the dienone-phenol rearrangement of 1,4-androstadiene-3,17-dione (3) was 1-methylestrone-16-sulfonic acid.

SUMMIT, NEW JERSEY

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CATALYTIC HYDROGENATION OF SOME ARYL-SUBSTITUTED ALIPHATIC ACIDS

NATHAN L. SMITH AND FRANCIS L. SCHMEHL¹

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In the course of an investigation of cyclohexyl-substituted aliphatic acids, the following were derived from the corresponding aryl derivative by catalytic reduction: cyclohexylstearic acid, *p*-cyclohexylcyclohexylstearic acid, *p*-dodecylcyclohexylstearic acid, and cyclohexylundecanoic acid. The arylstearic acids are a mixture of about equal parts of the 9- and 10-substituted acid prepared by the Friedel and Crafts reaction of the olefinic acid and an aromatic compound (1, 2, 3). The arylundecanoic acid is prepared by the same reaction and the product is a mixture of the 10- and 11-substituted acid (4). Aqueous potassium permanganate oxidation demonstrated the presence of para-oriented arylstearic acids (1).

Smith, Alderman, and Nadig (5) reduced phenyl-substituted aliphatic acids, with up to five carbon atoms in the chain, in a quantitative study of catalytic hydrogenation. This was an elaboration of the qualitative investigation of some of these compounds by Adams and Marshall (6). The hydrogenation of the benzene nucleus in these investigations was conducted in a solution of acetic acid with a platinum catalyst at room temperature (or slightly elevated) and a hydrogen pressure of several atmospheres. Baker and Schuetz (7) found that simple benzenoid hydrocarbons were reduced at high hydrogen pressure under the influence of Adams catalyst. The reduction proceeds readily at room temperature. Adkins (8) evaluated the reduction of the benzene ring with nickel catalysts.

The present work extends the investigation of the catalytic hydrogenation of the benzenoid structure in aralkyl acids with regard to compounds with greater length of aliphatic chain and more complex substitution on the aromatic ring. It was found that with increased molecular complexity larger amounts of catalysts, higher hydrogen pressure, and longer time favored complete reduction (6). Purified starting materials were necessary for successful hydrogenation of the aryl-substituted aliphatic acids. Purification of the acids was attained by refluxing an alcoholic solution of the starting materials with Raney nickel. It was recalled that in the preparation of these acids the aromatic component was usually a commercially available product frequently contaminated with difficultly removable organic sulfur impurities. The poisoning of hydrogenation catalysts from this and other causes has been previously reported and remedial methods devised (9, 10).

¹ Present address: National Institute of Health, Washington, D. C.

TABLE I
CATALYTIC HYDROGENATION OF ARYL-SUBSTITUTED ALIPHATIC ACIDS

STARTING ACID ^f	MOLES	°C.	HRS.	CATALYST ^g	ACID PRODUCT ^f
Phenylstearic.....	0.57	165	5	Ni(R)	Cyclohexylstearic
Phenylstearic.....	.20	200	2	UOP	Cyclohexylstearic
Phenylstearic.....	.20	200	3	UOP ^b	Cyclohexylstearic
<i>p</i> -Xenylstearic.....	.10	165	5	Ni(R)	<i>p</i> -Cyclohexylcyclohexylstearic
<i>p</i> -Xenylstearic.....	.06	200	4	UOP	<i>p</i> -Cyclohexylcyclohexylstearic
<i>p</i> -Dodecylphenylstearic....	.08	240	4	Ni(R)	<i>p</i> -Dodecylcyclohexylstearic
Phenylundecanoic.....	.05	85	18	PtO ₂ ^c	Cyclohexylundecanoic
Phenylundecanoic.....	.07	80	1	PtO ₂ ^d	Cyclohexylundecanoic
Phenylundecanoic.....	.38	230	5	Ni(R)	Cyclohexylundecanoic
Phenylundecanoic.....	.59	150	2	UOP ^e	Cyclohexylundecanoic

* Unless otherwise noted, the initial hydrogen pressure varied between 175 to 200 atmospheres. The UOP catalyst, which is essentially nickel on kieselguhr, was obtained from Universal Products Company, Riverside, Illinois.

^b Dioxane was used as solvent.

^c The hydrogenation was incomplete. In this reaction glacial acetic acid was used as solvent and the initial hydrogen pressure was four atmospheres.

^d Glacial acetic acid was used as solvent.

^e The UOP catalyst was pulverized before use; the unpulverized, $\frac{1}{8}$ " pellets failed to catalyze this reaction.

^f The substituted stearic acids are mixtures of the 9- and 10-isomers. The substituted undecanoic acids are mixtures of the 10- and 11-isomers.

TABLE II
SOME PHYSICAL CONSTANTS OF THE STARTING MATERIALS AND HYDROGENATION PRODUCTS
ARYL-SUBSTITUTED ALIPHATIC ACIDS^{a, b}

	B.P., °C.	MM.	n _D ²⁰	NEUTRALIZATION EQUIVALENT	
				Found	Theory
Phenylstearic.....	207-220	0.4	1.4881	356	360
<i>p</i> -Xenylstearic.....	258-278	1.2	1.5290	441	437
<i>p</i> -Dodecylphenylstearic.....	220-235	1.0	1.4980	540	529
Phenylundecanoic.....	165-173	0.5	1.4960	276	262

ALICYCLIC-SUBSTITUTED ALIPHATIC ACIDS^{a, b}

Cyclohexylstearic	201-205	0.1	1.4713	371	366
<i>p</i> -Cyclohexylcyclohexylstearic.....	209-228	0.3	1.4888	450	443
<i>p</i> -Dodecylcyclohexylstearic.....	176-196	0.3	1.4787	540	535
Cyclohexylundecanoic.....	140-142	0.2	1.4768	270	268

* Data are for the purified material.

^b The substituted stearic acids are mixtures of 9- and 10-substituted acids. The substituted undecanoic acids are mixtures of 10- and 11-substituted acids.

EXPERIMENTAL

The general method adopted here for the preparation of the cyclohexyl-substituted aliphatic acids was as follows: An alcoholic solution of the aryl-substituted acid^{1,2} was heated under reflux for six hours with approximately 20% (by weight) of Raney nickel. The catalyst was removed by sintered-glass filtration or centrifugation and the solvent distilled under water-pump vacuum. The resulting acid was then fractionated in vacuum.

High pressure hydrogenations were conducted in an electrically heated bomb (185 or 300 ml. capacity) mounted in a mechanical rocker (American Instrument Company). Glass liners for these bombs were omitted after preliminary runs indicated that a liner was not needed. Low pressure reactions were carried out in a conventional Parr shaking apparatus equipped with a heat-jacketed reaction bottle. Unless otherwise noted, no solvent was used. Approximately 10% of catalyst was employed throughout the investigation.

At the completion of the reaction the mixture was removed from the bomb with benzene. The catalyst was freed from the mixture and the solvent removed by water-pump vacuum. The reduced acid was then fractionated in vacuum.

Table I indicates the conditions for the hydrogenation of the aryl-substituted aliphatic acids. Table II shows some of the properties of the cyclohexyl-substituted aliphatic acids prepared in this investigation. Each compound is characterized by the boiling point, refractive index, and neutralization equivalent. The expected decreased values for refractive index and boiling point were observed in the hydrogenation products. The refractive index decrease for the reduced monobenzenoid structure is approximately .02 and for the dibenzenoid ring is .04. Apparently, the mixed isomers of the starting material hinder the formation of crystalline derivatives since no solid products were obtained. The yield in most cases was essentially quantitative.

WASHINGTON 20, D.C.

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¹ The arylstearic acids were supplied by the Eastern Regional Research Laboratory of the Department of Agriculture and are described in publications by that Laboratory (1, 2, 11).

² The phenylundecanoic acid was an Eastman Kodak Company product.

STUDIES IN SILICO-ORGANIC COMPOUNDS. VII. THE PREPARATION AND PROPERTIES OF CERTAIN SUBSTITUTED SILANES¹

JAMES W. JENKINS, NALO L. LAVERY, PAUL R. GUENTHER,
AND HOWARD W. POST

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INTRODUCTION

It was the purpose of this work to prepare certain simple derivatives of silane of the general formulas RSiHCl_2 , R_2SiHCl , and R_3SiH to be used later in more extensive work covering their properties. Interaction of trichlorosilane with organometallic compounds was selected as the method of preparation.

Pape (1, 2) prepared two types of silanes by the use of zinc dipropyl:



Taurke (3) and Ladenburg (4) continued the work. Triphenylsilane has been prepared through the action of the Grignard reagent (5) and through the medium of a lithium derivative (6):



Other references complete the bibliography (7 through 17).

In 1885, Polis (20) prepared tetraphenylsilane, tetra-*p*-tolylsilane and tetra-benzylsilane by the interaction of the proper chloride, tetrachlorosilane, and sodium. Triphenylchlorosilane reacts with sodium (21) to form hexaphenyl-disilane, and 1,3-diethyl-1,3-diphenyl-1,3-dipropyldisilane has been prepared by the action of sodium on ethylphenylpropylchlorosilane (22). On the other hand, Kipping and Steele (23) reported that the action of sodium on dibenzyl-dichlorosilane at the boiling point of toluene produced tetrabenzylsilane. Kraus and Nelson (7) prepared hexaethyldisilane by the interaction of sodium and triethylbromosilane. Other work followed (24, 25, 26). The use of lithium metal in syntheses of silicon compounds of these types has also been investigated (6, 9, 27, 28, 29, 30).

DISCUSSION

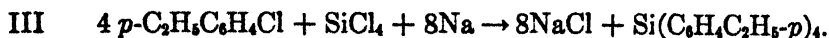
In view of the high degree of reactivity of the chlorine atoms in trichlorosilane it was felt that the Grignard reagents, in cases where these were used, should be added in high dilution. The work of Kraus and Nelson (7) was here repeated with satisfactory yields of triethylsilane. Interaction of 0.6 mole of benzyl-magnesium chloride and 0.1 mole of trichlorosilane produced tribenzylsilane in good yields. The silicon compound was added to the Grignard. Adding in reverse order and decreasing the molar ratio of Grignard to trichlorosilane resulted in the preparation of benzyl-dichlorosilane and dibenzylchlorosilane.

¹ The work on which this paper is based comprises a portion of a program being carried out under contract with the Office of Naval Research.

Dibenzyl was frequently observed as a by-product. The use of Grignard reagents which contained bromide was avoided whenever only partial replacement of chlorines was desired because of the possibility of halogen interchange.

The preparation of allylmagnesium bromide proceeded smoothly. Good yields of triallylsilane were obtained from the interaction of this reagent with trichlorosilane.

Using the method of Polis (20), *p*-ethylchlorobenzene, sodium, and tetrachlorosilane were allowed to react with the production of tetra-*p*-ethylphenylsilane:



When Taurke's (3) method for the preparation of similar derivatives of trichlorosilane was used, only tetra-*p*-ethylphenylsilane was isolated. Here, sodium,

TABLE I
PHYSICAL PROPERTIES

SUBSTANCE	B.P., °C	M.P., °C	<i>d</i>	<i>n</i> _D
HSi(C ₂ H ₅) ₃	105-115			
HSi(CH ₃ C ₆ H ₅) ₃	200-210	90-91		
(C ₆ H ₅ CH ₂) ₃ SiHCl*	155-151 (6 mm.)		1.0863(20°/20°)	1.5734(20°/D)
C ₆ H ₅ CH ₂ SiHCl ₂ *	53-55 (2 mm.)		1.1770(27°/27°)	1.5316(20°/D)
HSi(CH ₂ CH=CH ₂) ₃ *	160-165		0.8705(25°/25°)	1.4678(25°/D)
Si(C ₆ H ₄ C ₂ H ₅ - <i>p</i>) ₄ *		199-201		

* New compound.

trichlorosilane and *p*-ethylchlorobenzene were allowed to interact with ethyl acetate as the catalyst. Tetra-*p*-ethylphenylsilane was the only product when the experiments were repeated using hexachlorodisilane. No results were obtained with *m*-ethylchlorobenzene or with *o*-ethylchlorobenzene. Similar attempts to prepare tetra-*p*-propylphenylsilane and tetra-*p*-butylphenylsilane were unsuccessful. Lithium, trichlorosilane, and *p*-ethylchlorosilane reacting, produced only a small amount of tetra-*p*-ethylphenylsilane.

EXPERIMENTAL PART

Triethylsilane. Trichlorosilane (5 cc. 0.05 mole) in 100 cc. of anhydrous ether was added dropwise to 50 cc. (0.15 mole) of ethylmagnesium chloride in 100 cc. of anhydrous ether with cooling to 0° and stirring. The system was allowed to warm up to room temperature and was refluxed for eight hours with constant stirring. Ice-water, 100 cc., containing 5 cc. of sulfuric acid was added. The ether layer was removed and dried over calcium chloride. Distillation yielded 3 cc., b.p. 105-115°, soluble in acetone and 95% ethanol. The product evolved hydrogen when treated with warm alcoholic sodium hydroxide. A repetition of this run using double quantities yielded 10 cc. of triethylsilane.

Tribenzylsilane. Trichlorosilane (10 cc., 0.1 mole) in 100 cc. of anhydrous ether was added dropwise to 300 cc. (0.6 mole) of benzylmagnesium chloride in ether with constant stirring. The system was kept at 0°. After standing sixty-six hours the mixture was refluxed for twenty-three hours. Acidified water was added and the ether layer separated.

After distillation of the ether and cooling, white crystals appeared, m.p. 91° , yield 67%, mol. wt. (cryoscopic from benzene) 309; calc'd, 302. Hydrogen was evolved with sodium hydroxide in ethanol. On repetition using 0.3 mole of benzylmagnesium chloride and 0.1 mole of trichlorosilane the entire reaction mixture was filtered by suction and the ethereal solution distilled. There were obtained crystals, b.p. $150-160^{\circ}$ (22 mm.), m.p. $52-53^{\circ}$ and a non-distillable residue. The crystals were dibenzyl. After three days, crystals of tribenzylsilane deposited from the residue, m.p. 90° . Benzylmagnesium chloride (0.2 mole) in anhydrous ether was added dropwise to 10 cc. (0.1 mole) of trichlorosilane in 400 cc. of anhydrous ether with stirring at 0° . The system was allowed to stand at room temperatures for sixty-four hours, then refluxed for four hours. Vacuum distillation of the ether layer produced 7 cc. of a colorless liquid, b.p. $200-210^{\circ}$ which crystallized on cooling, m.p. 90° , tribenzylsilane. A small amount (2 cc.) of a low-boiling product was obtained, Cl (found) 4.93; calc'd dibenzylchlorosilane, 14.4.

Dibenzylchlorosilane. From the interaction of 0.6 mole of benzylmagnesium chloride in anhydrous ether and 0.3 mole of trichlorosilane, also in anhydrous ether, there was formed after seventeen hours standing and eight hours refluxing, 26 cc. of a colorless liquid b.p. $155-161^{\circ}$ (6 mm.), Cl (found) 13.77; calc'd dibenzylchlorosilane, 14.4: $d(20^{\circ}/20^{\circ}) = 1.0863$, $n(20^{\circ}/D) = 1.5734$. Tribenzylsilane was isolated from the residue.

Benzylidichlorosilane. When benzylmagnesium chloride and trichlorosilane reacted as above but in the molar ratio of 1:1, there was obtained 10 cc. of a distillate, b.p. $53-55^{\circ}$ (2 mm.), Cl (found) 37.58, 37.70; calc'd benzylidichlorosilane, 37.20; $n(20^{\circ}/D) = 1.5316$, $d(27^{\circ}/27^{\circ}) = 1.1770$. Subsequent runs confirmed these results, with the formation of dibenzylchlorosilane as well. At times isolable amounts of tribenzylsilane were also formed here.

Triallylsilane. A three-neck, 3-liter flask filled with anhydrous ether was used to prepare 1.0 mole of the Grignard reagent made from allyl bromide and magnesium. After forty-eight hours, 0.1 mole of trichlorosilane was added dropwise, diluted with about five volumes of anhydrous ether. The reaction commenced immediately without preheating, in fact ice cooling was necessary throughout. After one hour, the system was refluxed for twelve hours, with formation of a grey pasty mass on the sides of the flask. Excess Grignard reagent was destroyed by the addition of 100 cc. of ice and water slightly acidified with 15 cc. of sulfuric acid. The ether extract of this mixture, dried over calcium chloride, yielded fractions b.p. $75-80^{\circ}$ and $155-165^{\circ}$. Subsequent runs showed increased yields. It was later found that instead of a 10:1 molar ratio of Grignard reagent to trichlorosilane, 8:1 proved sufficient. The first fraction was allyl bromide, the second b.p. $160-165^{\circ}$ was triallylsilane. Triallylsilane has a mint-like odor, is flammable with a smoky flame, $d(25^{\circ}/25^{\circ}) = 0.8705$, $n(25^{\circ}/D) = 1.4678$, insoluble in water, neutral, soluble in acetone, ether, and alcohol. Triallylsilane reacted violently with concentrated sulfuric acid with evolution of smoke and formation of a black mass. Silver in silver nitrate was reduced to a black powder. Hydrogen gas was evolved on treatment with alcoholic potassium hydroxide. Mol Wt. (cryoscopic from benzene) 144; calc'd, 152.

Tetra-*p*-ethylphenylsilane. Thinly sliced sodium (11.5 g., 0.5 mole) under 150 cc. of anhydrous ether was treated with 35 g. (0.25 mole) of *p*-ethylphenylchlorobenzene in 100 cc. of anhydrous ether. Under continuous stirring and cooling in an ice-bath, 10.6 g. (0.063 mole) of tetrachlorosilane was added. The reaction proceeded by itself for about two hours and was brought to completion by the heat of a water-bath. A blue color developed and a blue precipitate separated. After standing overnight, the reaction mixture was filtered and the remaining liquid cooled to 10° for twelve hours. Long needles appeared and were purified from ether, weight 8 g., m.p. $199-201^{\circ}$, Si (found) 6.66, 5.98; calc'd, tetra-*p*-ethylphenylsilane, 6.26, mol. wt., (cryoscopic from benzene) 432.0, 451.0; calc'd, 448.5. In a similar manner, using 0.25 mole of trichlorosilane, 4.0 g. of tetra-*p*-ethylphenylsilane were obtained, m.p. $190-201^{\circ}$, m.p. (mixed with first sample) $198-201^{\circ}$, mol. wt., (cryoscopic from benzene) 460.5. Repetition of the experiment using 0.041 mole of hexachlorodisilane and 3 cc. of ethyl acetate as catalyst produced 5 g. of tetra-*p*-ethylphenylsilane, m.p. $199-201^{\circ}$, mol. wt. (cryoscopic from benzene) 465.

Butylbenzene was prepared by the interaction of 141 g. of bromobenzene, 123 g. of butyl bromide, and 57.6 g. of sodium in 200 cc. of anhydrous ether. A vigorous reaction set in which proceeded for three hours without application of heat. A blue precipitate formed and the sodium was covered with a blue deposit. The reaction mixture was then refluxed for five hours and filtered. Butylbenzene b.p. 175–179° (750 mm.), 53 g.

p-Butylchlorobenzene was formed when butylbenzene was subjected to the action of a stream of chlorine gas with iron nails as catalyst. The reaction flask was surrounded by an ice-bath while the chlorine was bubbled through the hydrocarbon. *p*-Butylchlorobenzene, b.p. 220–223° (751 mm.), 217–224° (748 mm.), average yield 72%, b.p. [literature (31) 225–228° (761 mm.)].

p-Propylchlorobenzene was prepared as was the butyl compound above, b.p. 195–198° (758 mm.), [literature (32) 190–192° (760 mm.)].

Trichlorosilane was obtained from a reliable source. Its physical properties were satisfactory.

Ethylmagnesium chloride was purchased from Arapahoe Chemicals Inc., Boulder, Colorado.

Benzylmagnesium chloride was prepared in this laboratory by the usual procedure.

Diethyl ether was made anhydrous by further drying the purchased anhydrous grade over sodium and distilling.

Chlorine was determined by the method of Rochow (19).

Silicon was determined by the perchloric acid method.

SUMMARY

1. The preparation of triethylsilane has been repeated with good yields.
2. The interaction of benzylmagnesium chloride and trichlorosilane in molar proportions varying from 6:1 to 1:1 produces tribenzylsilane, dibenzylchlorosilane, and benzyldichlorosilane. Dibenzyl is formed in small amounts as a by-product.
3. The preparation of triallylsilane through the interaction of allylmagnesium bromide and trichlorosilane is reported and the physical properties of the product are described.
4. Tetra-*p*-ethylphenylsilane can be prepared by the action of *p*-ethylchlorobenzene and sodium on tetrachlorosilane. The ortho and meta isomers have not been prepared by this method nor have the corresponding *p*-propyl and *p*-butyl derivatives.
5. When trichlorosilane or hexachlorodisilane is used instead of tetrachlorosilane in the above synthesis, tetra-*p*-ethylphenylsilane is the only product formed under the conditions set forth herein.

BUFFALO 14, N. Y.

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STEROLS OF MARINE MOLLUSKS. II. THE STEROLS OF THE PERIWINKLE, *LITTORINA LITTOREA*¹

C. ALBERT KIND AND STEDMAN C. HERMAN

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Bergmann and Low have recently called attention to the constancy in fat content and nonsaponifiable matter exhibited by marine mollusks (1). On the basis of available data it appears that the gastropods invariably contain cholesterol as the principal sterol although sterols of other orders (C_{28} , C_{29}) may be present as minor components of the mixtures which are so frequently obtained.

The first paper in the present series (2) has described the isolation of cholesterol from two marine gastropods. In the case of the *Nassa obsoleta* a second component of the mixture was isolated but not identified due to a lack of material. It was suggested that this substance might be clionasterol, first isolated from sponges (3, 4), and later reported as present in a species of gorgonia (5). Clionasterol has now been definitely characterized as a minor component of the sterol fraction of the *Littorina littorea*, and it therefore seems likely that it is also present in the closely related *Nassa*.

The marine snail, *Littorina littorea*, is one of the common mollusks of the New England coast and is readily obtainable in large quantities. The material used in the present work was obtained from the Marine Biological Laboratory at Woods Hole, Massachusetts. The nonsaponifiable matter melted at 130–135° and consisted of 61% sterol determined by precipitation with digitonin. Acetylation and subsequent bromination yielded insoluble acetate bromides which decomposed on standing. Attempts to prepare the steryl bromides likewise led to the formation of unstable products. Benzoylation of the crude sterol however yielded a product which was only partially soluble in hot ethanol, a behavior which had previously been observed in the case of the benzoate prepared from the nonsaponifiable matter of the *Nassa obsoleta*. A series of fractional crystallizations from absolute alcohol led to the separation of cholesteryl benzoate as the least soluble component, constituting about 85% of the mixture. This was further identified by conversion to the free sterol and the acetate. The occurrence of cholesterol in such a high proportion lends further support to the contention of Bergmann and Low regarding the significance of this sterol in gastropods. Concentration of the mother liquors yielded a material which after purification melted at 133–135°. The behavior of this benzoate during cooling from the melt was similar to that described for clionasteryl benzoate (4). The free sterol melted at 137–138° and exhibited a specific rotation in agreement with that reported for clionasterol.

The occurrence of clionasterol in the *Littorina* is significant because of the bearing it may have on the structure of the "periwinkle" provitamin D reported

¹ This work was aided by a grant from the University of Connecticut Research Fund.

by previous workers. Bock and Wetter have determined the provitamin D content to be 9.6% based on spectroscopic evidence (6). Boer *et al.* (7) have isolated the crystalline provitamin and determined the potency of the irradiation product. On the basis of the present findings, the provitamin would be expected to be related either to cholesterol or to clionasterol. The data in Table I show clearly that the provitamin is not 7-dehydrocholesterol. Comparison with 7-dehydroclionasterol, prepared by Bergmann, Lyon, and McLean (8), shows close agreement in melting points of both the sterol and the acetate. Although the optical rotations do not appear to be in agreement, the fact that Boer *et al.* used benzene instead of chloroform as the solvent may account for the discrepancy. We were unable to obtain a sample of 7-dehydroclionasterol to determine the solvent effect but it is of interest to note that 7-dehydrocholesterol obtained by Boer *et al.* (9), gave $(\alpha)_D -127^\circ$ (benzene), as compared with -113.6°

TABLE I
COMPARISON OF THE LITTORINA PROVITAMIN D WITH 7-DEHYDROCHOLESTEROL AND 7-DEHYDROCLIONASTEROL

	STEROL		ACETATE	
	M.P., °C.	$(\alpha)_D$	M.P., °C.	$(\alpha)_D$
7-Dehydrocholesterol. . . .	143	-114	129	-85
7-Dehydroclionasterol. . . .	138	-98	139	-72
Periwinkle provitamin. . . .	137	-124*	136	-85*

* Rotation taken in benzene.

(chloroform) obtained by Windaus, Lettré, and Schenck (10) for the synthetic compound. The data in Table I therefore suggest to us that the provitamin of the *Littorina* is identical with 7-dehydroclionasterol.

EXPERIMENTAL

Isolation of the sterol mixture. Thirty-six kilograms of meat and shells was pulverized and air-dried for a period of several weeks. Batches of about four kilograms were further dehydrated with acetone in a Soxhlet apparatus and then exhaustively extracted with ether. The solvents were removed and the extracts were saponified in the usual manner. The nonsaponifiable matter consisted of 8.1 g. of a light yellow crystalline solid which melted at $130-135^\circ$ and gave a positive Liebermann-Burchard reaction.

To a solution of 204 mg. of crude sterol in ethanol was added 60 cc. of a one per cent solution of digitonin in ethanol. The digitonide was cleaved by Bergmann's procedure (11) yielding 125 mg. of sterol which melted at $133-137^\circ$.

Preparation of the benzoates. To a solution of 2.5 g. of crude sterol in dry pyridine was added 4 cc. of benzoyl chloride and the mixture allowed to stand for 48 hours. The benzoates were precipitated with water, filtered, and washed with cold ethanol. A series of ten fractional crystallizations from absolute alcohol yielded 0.86 g. of benzoate which melted to a turbid liquid at 146° and cleared at 174° . When mixed with cholesteryl benzoate there was no depression of the melting point. $(\alpha)_D^{25} -16.6^\circ$ (34.3 mg. in 3 cc. of chloroform gave an α reading of -0.19°).

Saponification of the benzoate yielded cholesterol, m.p. $147-148^\circ$. $(\alpha)_D^{25} -38.0^\circ$ (36.4 mg. in 3 cc. of chloroform gave an α reading of -0.46°).

Anal. Calc'd for, $C_{27}H_{46}O$: C, 83.87; H, 11.99.

Found: C, 83.80; H, 11.75.

Acetylation with acetic anhydride gave cholesteryl acetate, m.p. 114°. The acetate gave no depression in melting point when mixed with authentic material.

Clionasterol. Concentration of the mother liquors from the separation of cholesteryl benzoate yielded 0.162 g. of material. This was crystallized eleven times from 95% ethanol, and melted at 133–135°. On cooling, the benzoate momentarily changed to a green-blue at 115° and solidified at 106°. (α_D^{25} -17.8° (40.2 mg. in 3 cc. of chloroform gave an α reading of -0.24°). When mixed with clionasteryl benzoate³ the melting point was 133–134°.

Anal. Calc'd for $C_{30}H_{48}O_2$: C, 83.33; H, 10.49.

Found: C, 83.09; H, 10.54.

Saponification of the benzoate yielded clionasterol, m.p. 137–138°. (α_D^{25} -37.7° (21.5 mg. in 3 cc. of chloroform gave an α reading of -0.26°). When mixed with authentic clionasterol³ the melting point was 137–138°.

Anal. Calc'd for $C_{27}H_{46}O$: C, 83.99; H, 12.15.

Found: C, 84.37; H, 12.08.

SUMMARY

An examination of the sterol mixture obtained from the periwinkle, *Littorina littorea* has revealed the presence of cholesterol and clionasterol. These components were separated by fractional crystallization of the mixed benzoates from absolute alcohol.

This report describes the first observation of the presence of clionasterol in mollusks. It has been suggested that the isolation of this sterol may shed light on the nature of the "periwinkle provitamin D". Evidence for the identity of the provitamin with 7-dehydroclionasterol has been presented.

The results also confirm the suggestion that gastropod mollusks contain cholesterol as the principal sterol.

STORRS, CONN.

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³ The authors are indebted to Prof. Werner Bergmann for the samples of clionasterol and clionasterol benzoate.

STUDIES IN THE JUGLONE SERIES. II. HYDROXY AND HYDROXYHALOGENO DERIVATIVES

R. H. THOMSON

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It was shown in Part I (1) that the structures assigned by previous workers to certain halogen derivatives of juglone were incorrect. A search of the literature has revealed a number of other derivatives of unknown or uncertain constitution, and these have now been investigated.

A hydroxyjuglone was obtained by Mylius (2) by oxidation of juglone, or better, α -hydrojuglone, in alkaline solution, and also by acid hydrolysis of dimethylaminojuglone. The products obtained had very similar physical properties and it was concluded that they were identical. The position of the hydroxyl group was not indicated.¹ Repetition of this work yielded the compounds described by Mylius, but a mixed melting point determination showed a marked depression,² and the non-identity of these substances was clearly shown by the preparation of their diacetates, whose melting points differed by 15°. The structure of these two substances has now been established by hydrolysis of 2- and 3-anilinojuglone to give the corresponding hydroxyjuglones, which were compared with Mylius' substances. The product obtained by oxidation of juglone was found to be identical with 3-hydroxyjuglone, and the compound derived from dimethylaminojuglone proved to be 2-hydroxyjuglone. This also establishes the structure of the dimethylamino derivative, and of the anilino derivative obtained by Mylius by reaction of 3-hydroxyjuglone with aniline (2). 3-Hydroxyjuglone is best prepared from 3-chlorojuglone by reaction with sodium hydroxide, but the 2-isomer cannot be obtained in this way. A hydroxyjuglone was also obtained by Fieser and Dunn (4) by Thiele acetylation of juglone to give a tetraacetoxynaphthalene, followed by hydrolysis and oxidation. On repeating this, the product obtained was found to be identical with 3-hydroxyjuglone. The tetraacetoxynaphthalene is therefore the 1,3,4,5-isomer.

By reaction of 2,3-dichloro- and 2,3-dibromo-juglone with sodium hydroxide (5, 6), one halogen atom is replaced, and the chloro product was regarded by Wheeler, Dawson, and McEwen (5) as 3-chloro-2-hydroxyjuglone. 2,3-Dichlorojuglone reacts with aniline to give 2-anilino-3-chlorojuglone (1), acid hydrolysis of which should yield the chlorohydroxy compound of Wheeler *et al.* This was not the case, however, and a new chlorohydroxyjuglone was isolated. The two isomers were also obtained by chlorination of 2- and 3-hydroxyjuglone and could therefore be identified. It was thus confirmed that the product obtained by hydrolysis of the anilino derivative was 3-chloro-2-hydroxyjuglone,

¹ Certain workers (3, 13), have regarded the compound obtained by the oxidation method as 2-hydroxyjuglone.

² Liebermann (9) in 1877, appears to have been the first to record the use of mixed melting point determinations, but Mylius (1885) seems to have overlooked this.

whilst the compound formed by reaction of 2,3-dichlorojuglone with sodium hydroxide was 2-chloro-3-hydroxyjuglone. The corresponding bromohydroxyjuglones were derived from 2,3-dibromojuglone, and were readily converted to chlorohydroxyjuglones by the action of alcoholic hydrochloric acid. According to Wheeler and Naiman (6) crystallization of 2-bromo-3-hydroxyjuglone from aqueous alcohol yields a red monohydrate. This has not been investigated but it may be mentioned that all the halogenohydroxyjuglones so far examined form yellow to orange solutions in alcohol, which become red on addition of water, and similarly, alcoholic solutions of their diacetates, which are pale yellow, redden when diluted with water. In all cases, addition of a trace of mineral acid restores the yellow color. 2- and 3-Hydroxyjuglones do not behave in this way.

Bromination of juglone with excess bromine affords 2,3,6-tribromojuglone (1). The behavior of this compound was studied by Wheeler *et al.* (7, 8), who found that reaction with sodium hydroxide, hydrochloric acid, aniline, and other amines, replaced only one bromine atom. They argued that one bromine atom must therefore have a different environment from the other two, and hence it must be the bromine atom in the benzenoid ring which is involved in the above reactions. However, as was found later by Wheeler and his co-workers, 2,3-dichloro- and 2,3-dibromo-juglone behave in the same way (5, 8), and it has now been shown that the labile bromine atoms of tribromojuglone are in the quinonoid ring. Thus, the product obtained by reaction of 2,3,6-tribromojuglone with sodium hydroxide was also formed by further bromination of 2-bromo-3-hydroxyjuglone, and its structure is consequently 2,6-dibromo-3-hydroxyjuglone (I). The constitutions of certain reduction products derived from this compound now call for correction: in particular the compound obtained by reduction with zinc dust in alkaline solution, regarded by Wheeler *et al.* as 1,4,5,8-tetrahydroxynaphthalene (8),³ is the 1,3,4,5-isomer. The anilino derivative obtained by reaction of 2,3,6-tribromojuglone with aniline yielded on acid hydrolysis a dibromohydroxyjuglone different from that already described. This was also obtained by bromination of 3-bromo-2-hydroxyjuglone and its structure is thus 3,6-dibromo-2-hydroxyjuglone, the anilino derivative being 2-anilino-3,6-dibromojuglone (II).

Wheeler and Naiman (6) readily converted 2,3-dibromojuglone into 2,3-dichlorojuglone by warming with a large excess of alcoholic hydrochloric acid, but by a similar treatment of 2,3,6-tribromojuglone using an even larger excess of hydrochloric acid, Wheeler and Scott (7) obtained a product which, surprisingly, they considered to be a dibromomonochlorojuglone. This claim was supported by a complete elementary analysis of the compound, and also of the acetyl derivative, although it may be noted that in the latter case the halogen figures were derived from insufficient data (8). On repeating this work, a compound was obtained which was undoubtedly that described by Wheeler and Scott but analysis showed it to be a dichloromonobromojuglone.⁴ This would be expected by

³ This structure has already been shown to be incorrect by Dimroth and Roos (11).

⁴ The acetate had m.p. 172° whereas Wheeler and Andrews record m.p. 159.5–160°. Several other discrepancies in melting point of this order have been observed. See experimental section of this paper and (10).

unsuccessful. This recalls the failure of Wheeler, Dawson, and McEwen (5) to chlorinate 2,3-dichlorojuglone, in marked contrast to the ease with which juglone takes up three atoms of bromine.

In this series, compounds possessing identical structures but different halogen atoms frequently have similar melting points, and mixtures of the two usually melt at intermediate temperatures; in such cases a mixed melting point determination is an unreliable criterion of identity. This applies particularly to halogenohydroxyjuglones and their diacetates. Examples are given in Table I.

The structures of two further compounds remain to be elucidated. Wheeler and Andrews (8) attempted to prepare tribromojuglone ethers by interaction of ethyl and methyl iodides with the sodium salt of tribromojuglone in alcoholic

TABLE I
MIXED MELTING POINTS WHICH ARE UNRELIABLE CRITERIA OF IDENTITY

COMPOUND	M.P., °C.	MIXED M.P., °C.
2-Chloro-3-hydroxyjuglone	193	193
2-Bromo-3-hydroxyjuglone	194	
2-Chloro-3-hydroxyjuglone diacetate	147	146-147
2-Bromo-3-hydroxyjuglone diacetate	146	
3-Chloro-2-hydroxyjuglone	224	212-213
3-Bromo-2-hydroxyjuglone	217	
3-Chloro-2-hydroxyjuglone diacetate	157	158-159
3-Bromo-2-hydroxyjuglone diacetate	164	
6-Bromo-2-chloro-3-hydroxyjuglone	255	246-247
2,6-Dibromo-3-hydroxyjuglone	241	
6-Bromo-2-chloro-3-hydroxyjuglone diacetate	170	174-175
2,6-Dibromo-3-hydroxyjuglone diacetate	179	
2-Anilino-6-bromo-3-chlorojuglone	249	245-247
2-Anilino-3,6-dibromojuglone	244	
3-Chlorojuglone	166	169
3-Bromojuglone	172	
3-Chlorojuglone acetate	147	149
3-Bromojuglone acetate	151.5	

solution, but the reaction products contained only two atoms of bromine, the third being replaced by a hydroxyl group, and the compounds were regarded as 5-alkoxy-8-hydroxy-2,3-dibromo-1,4-naphthoquinones. The elimination of bromine, it was explained, was due to the action of the alcohol. Previously, Wheeler and Scott (7) had reported that tribromojuglone remained unchanged after boiling with alcohol for six hours, but Wheeler and Andrews claimed that an alcoholic solution of tribromojuglone gave a precipitate with silver nitrate after boiling for an unspecified time. The formation of alkoxyhydroxydibromonaphthoquinones has now been confirmed, but boiling alcohol has no effect on tribromojuglone, the latter being recovered unchanged after eighteen hours boiling. However the sodium salt of tribromojuglone reacts with ethyl and also with methyl alcohol to give the same ethoxy- and methoxy-hydroxydibromonaphthoquinones as Wheeler and Andrews obtained by reaction with alcoholic ethyl and

methyl iodides. In the preparation using alcoholic methyl iodide, the initial reaction product is the ethyl ether, which is slowly converted to the methyl ether on prolonged boiling. No reaction occurred when the sodium salt was refluxed with methyl iodide alone, or in dioxane solution, showing that the sodium salt does not react directly with methyl iodide. The conversion of the ethyl to the methyl ether, which was also achieved by refluxing a methyl alcoholic solution of the ethyl ether containing a trace of sodium, strongly suggested that the alkoxyl group was attached to the quinonoid ring. This was established conclusively by reaction with aniline, when both ethers gave 2-anilino-3,6-dibromojuglone, and by a facile hydrolysis with sodium hydroxide, which afforded 2-hydroxy-3,6-dibromojuglone. The ethers therefore have the structure 2-alkoxy-3,6-dibromojuglone, the ether group in the quinonoid ring having typical ester-like properties (12). As would be anticipated, the bromine atom at position 3 prevents esterification of 2-hydroxy-3,6-dibromojuglone by the Fischer-Speier method, but the methyl ether was easily obtained by methylation with diazomethane. The formation of the methyl ether by the Wheeler and Andrews method may be visualized as follows: the sodium salt (VI) reacts initially with ethyl alcohol to form tribromojuglone and sodium ethoxide, which further interact, the bromine atom at position 2 being replaced by an ethoxyl group (VII). Finally the ethyl ether reacts with methyl iodide to form the methyl ether (VIII). The trans-etherification (or trans-esterification) is possibly base-catalyzed, but the mechanism has not been studied. With regard to the formation of (VII), a similar reaction occurs when the sodium salt of tribromojuglone is boiled with water, a mixture of tribromojuglone and 2-hydroxy-3,6-dibromojuglone being obtained. Incomplete conversion to the hydroxy derivative is probably due to the low solubility of tribromojuglone in water. The presence of ethyl iodide in the preparation of 2-ethoxy-3,6-dibromojuglone by the Wheeler and Andrews method is superfluous.

EXPERIMENTAL

Microanalyses by Drs. G. Weiler and F. B. Strauss of Oxford. Melting points are uncorrected. Acetyl derivatives were prepared by the method given in Part I (1).

2-Hydroxyjuglone. (a) Hydrolysis of 2-dimethylaminojuglone according to Mylius (2); yield, 74%.

(b) Hydrolysis of 2-anilinojuglone(1). One gram of 2-anilinojuglone was dissolved in 15 cc. of concentrated sulfuric acid, and 15 cc. of water was added cautiously to the deep violet solution. The resulting dark red suspension was refluxed gently for five minutes until the color became dark brown. The mixture was then cooled, diluted with water, and filtered. The solid was extracted with 200 cc. of warm 2% aqueous sodium acetate, and the red extract acidified with dilute sulfuric acid. The yellow precipitate was collected and crystallized from dilute acetic acid; yield, 55%.

Both preparations yielded identical minute, light orange, needles, m.p. 220° (dec.), and formed identical diacetates which crystallized from methyl alcohol in elongated yellow plates, m.p. 152°.

5-Hydroxyjuglone. (a) Oxidation of α -hydrojuglone in alkaline solution with potassium ferricyanide as described by Mylius (2). The crude product was purified *via* the diacetate; yield, 9%.

(b) **Hydrolysis of 3-anilinojuglone (1).** A suspension of 0.5 g. of 3-anilinojuglone (finely divided) in 25 cc. of concentrated hydrochloric acid was refluxed for forty-five minutes, during which the reddish-violet color became a dark yellowish brown. After cooling, the suspension was diluted with water, and the solid collected and extracted with petrol (100-120°). The extract was concentrated to small bulk, from which orange plates separated on cooling; yield, 59%.

(c) **Thiele acetylation of juglone**, followed by hydrolysis and oxidation of 1,3,4,5-tetra-acetoxynaphthalene by the method of Fieser and Dunn (4). Juglone acetate separated twice during the acetylation period (ten days at room temperature) and was redissolved by warming; over-all yield, 52%.

(d) To a warm solution of 0.25 g. of 3-chlorojuglone in 20 cc. of alcohol, 10 cc. of 10% aqueous sodium hydroxide was added. The initial violet color rapidly changed to blood-red. After one hour on the water-bath the solution was cooled, diluted with 25 cc. of water, and acidified with dilute sulfuric acid. The reddish orange crystals which precipitated were collected and recrystallized from dilute acetic acid; yield, 79%.

All preparations yielded identical small, light orange plates, m.p. 218-220° (dec. after blackening from 210°), from dilute acetic acid, and formed identical diacetates which crystallized from methyl alcohol in fine pale yellow needles, m.p. 137°. A mixture of 2- and 3-hydroxyjuglone had m.p. 190°.

3-Chloro-2-hydroxyjuglone. (a) To a solution of 0.4 g. of 2-anilino-3-chlorojuglone in 6 cc. of concentrated sulfuric acid, 4 cc. of water was added cautiously. The suspension so obtained was refluxed gently for five minutes until the red color had disappeared. The resulting brown crystalline suspension was cooled, diluted with water, and the product collected and recrystallized from glacial acetic acid (charcoal); yield, 90%.

(b) A solution of 0.2 g. of 2-hydroxyjuglone in 4 cc. of glacial acetic acid containing 0.1 g. of chlorine was warmed on the water-bath for three hours, cooled, and poured into 50 cc. of cold water containing a little sulfuric acid. The yellow precipitate obtained was collected and crystallized from glacial acetic acid; yield, 67%.

(c) A solution of 0.2 g. of 3-bromo-2-hydroxyjuglone in 6 cc. of alcohol was warmed on the water-bath for one hour with 1.0 cc. of concentrated hydrochloric acid. Crystals of the chloro compound separated on cooling; yield, 90%.

All preparations yielded identical small glistening orange plates, m.p. 224°.

Anal. Calc'd for $C_{10}H_7ClO_4$: C, 53.45; H, 2.3; Cl, 15.8.

Found: C, 53.3; H, 2.3; Cl, 15.6.

All products formed identical diacetates which crystallized from alcohol in yellow needles, m.p. 157°.

3-Bromo-2-hydroxyjuglone. (a) Hydrolysis of 2-anilino-3-bromojuglone was carried out as described for the corresponding chloro compound.

(b) To a solution of 0.26 g. of 2-hydroxyjuglone in 10 cc. of glacial acetic acid, 0.065 cc. of bromine was added, and the solution warmed on the water-bath for two hours. Crystals separated on cooling, and were recrystallized from glacial acetic acid; yield, 71%.

Both preparations yielded identical orange-red needles, m.p. 217°.

Anal. Calc'd for $C_{10}H_7BrO_4$: C, 44.6; H, 1.85; Br, 29.75.

Found: C, 44.45; H, 2.05; Br, 29.6.

Both products formed identical diacetates which crystallized from alcohol in yellow needles, m.p. 164°.

2-Chloro-3-hydroxyjuglone. (a) This was obtained by reaction of 2,3-dichlorojuglone with sodium hydroxide as recorded by Wheeler, Dawson, and McEwen (5) who regarded it as 2-hydroxy-3-chlorojuglone.

(b) 3-Hydroxyjuglone was chlorinated in the same manner as 2-hydroxyjuglone.

(c) 2-Bromo-3-hydroxyjuglone was treated with alcoholic hydrochloric acid as described above for the isomeric compound. The product was isolated by dilution with water, and crystallized from carbon tetrachloride.

All preparations yielded clusters of identical orange-brown needles, m.p. 193° from

carbon tetrachloride, (Wheeler *et al.* report m.p. 191°) and formed identical diacetates, m.p. 147°, fine yellow needles from alcohol.

2-Bromo-3-hydroxyjuglone. (a) This was obtained by reaction of 2,3-dibromojuglone with sodium hydroxide according to Wheeler and Naiman (6).

(b) 3-Hydroxyjuglone was brominated in the same manner as 2-hydroxyjuglone. The product was isolated by pouring the solution into very dilute sulfuric acid, and crystallized from carbon tetrachloride.

Both preparations yielded identical fine, light orange, needles, m.p. 194° (Wheeler and Naiman record m.p. 192°).

Anal. Calc'd for $C_{10}H_6BrO_4$: C, 44.6; H, 1.85; Br, 29.75.

Found: C, 44.9; H, 1.9; Br, 29.55.

Both products formed identical diacetates which crystallized from alcohol in yellow needles, m.p. 146°.

3,6-Dibromo-2-hydroxyjuglone. (a) 2-Anilino-3,6-dibromojuglone was hydrolyzed with sulfuric acid in the usual way, and the crude product extracted with 2% aqueous sodium acetate; yield, 61%.

(b) A solution of 0.22 g. of 3-bromo-2-hydroxyjuglone in 2.2 cc. of glacial acetic acid was refluxed with 0.2 cc. of bromine for three hours. The crystals which separated on cooling were recrystallized from the same solvent; yield, 58%.

(c) To a hot solution of 0.25 g. of 2-methoxy-(or ethoxy)-3,6-dibromojuglone in 50 cc. of alcohol, 20 cc. of 10% aqueous sodium hydroxide was added. After warming for five minutes on the water-bath, the red solution was cooled, diluted with 70 cc. of water, and acidified with dilute sulfuric acid. The yellow precipitate was crystallized from glacial acetic acid; yield, 60%.

All preparations yielded identical orange needles, m.p. 206°.

Anal. Calc'd for $C_{10}H_4Br_2O_4$: C, 34.5; H, 1.15; Br, 46.0.

Found: C, 34.3; H, 1.5; Br, 45.7.

All products formed identical diacetates, m.p. 176°, yellow needles from alcohol.

2,6-Dibromo-3-hydroxyjuglone (I). (a) This was obtained by reaction of 2,3,6-tribromojuglone with sodium hydroxide by the method of Wheeler and Scott (7).

(b) 2-Bromo-3-hydroxyjuglone was brominated as described for the isomer.

Both preparations yielded golden brown prismatic needles, m.p. 241°, from glacial acetic acid. (Wheeler and Scott, who regarded this compound as 2,3-dibromo-8-hydroxyjuglone, recorded m.p. 236°). Wheeler and Andrews (8) prepared a monoacetate (presumably the 2-acetoxy compound) by boiling the material with a large excess of acetic anhydride for seventeen hours. A diacetate was readily obtained by boiling for one minute with twice its weight of acetic anhydride containing a trace of concentrated sulfuric acid. It crystallized from alcohol in clusters of yellow elongated plates, m.p. 179°.

Anal. Calc'd for $C_{10}H_4Br_2O_4$: C, 38.9; H, 1.85; Br, 37.0.

Found: C, 38.95; H, 1.95; Br, 37.2.

6-Bromo-2,3-dichlorojuglone (III). This was obtained by the method of Wheeler and Scott (7) who considered it to be 8-chloro-2,3-dibromojuglone. It crystallized from alcohol in red brown plates, m.p. 152°.

Anal. Calc'd for $C_{10}H_4BrCl_2O_4$: C, 37.3; H, 0.9.

Found: C, 37.5; H, 0.9.

The diacetate crystallized from alcohol in pale yellow needles, m.p. 172°. [Wheeler and Andrews (8) report m.p. 159.5–160°.]

Anal. Calc'd for $C_{12}H_4BrCl_2O_4$: C, 39.6; H, 1.4.

Found: C, 39.3; H, 1.55.

6-Bromo-2-chloro-3-hydroxyjuglone (IV). (a) An alcoholic solution of (III) was treated with excess sodium hydroxide by the usual method, the initial violet solution rapidly becoming blood-red. The product was crystallized from glacial acetic acid.

(b) 2,6-Dibromo-3-hydroxyjuglone was warmed with alcoholic hydrochloric acid in the usual manner. The bromochloro compound separated on cooling.

Both preparations yielded clusters of identical red brown prismatic needles, m.p. 255°, from glacial acetic acid.

Anal. Calc'd for $C_{10}H_5BrClO_4$: C, 39.55; H, 1.3.

Found: C, 39.7; H, 1.55.

Both products formed identical diacetates which separated from alcohol in minute yellow needles, m.p. 170°.

Anal. Calc'd for $C_{14}H_9BrClO_6$: C, 43.35; H, 2.1.

Found: C, 43.3; H, 2.25.

8-Anilino-3,6-dibromojuglone (II). (a) By reaction of 2,3,6-tribromojuglone with aniline according to Wheeler and Andrews (8) who considered it to be 8-anilino-2,3-dibromojuglone.

(b) A solution of 0.2 g. of 2-methoxy-3,6-dibromojuglone in 40 cc. of alcohol was refluxed with 0.1 cc. of aniline for twenty minutes. Crystals of the anilino derivative separated almost as soon as boiling commenced; yield, 94%.

Both products crystallized from methyl ethyl ketone in identical dark violet leaflets, m.p. 244°. (Wheeler and Andrews report m.p. 234.5–235.5°). The same product was obtained from 2-ethoxy-3,6-dibromojuglone.

Anal. Calc'd for $C_{11}H_9Br_2NO_2$: C, 45.4; H, 2.1; N, 3.3.

Found: C, 45.6; H, 2.4; N, 3.1.

8-Anilino-6-bromo-3-chlorojuglone (V). This was obtained from 6-bromo-2,3-dichlorojuglone as for (II) (a). It crystallized from methyl ethyl ketone in dark violet needles, m.p. 249°; yield, 68%.

Anal. Calc'd for $C_{11}H_8BrClNO_2$: C, 50.7; H, 2.4; N, 3.7.

Found: C, 50.6; H, 2.7; N, 3.85.

8-p-Toluidino-3,6-dibromojuglone. This was prepared by the method of Wheeler and Andrews (8). Crystallization from methyl ethyl ketone yielded dark violet rectangular plates, which appear black in the mass, m.p. 224°. (Wheeler and Andrews record m.p. 216–217°).

Anal. Calc'd for $C_{17}H_{11}Br_2NO_2$: C, 46.7; H, 2.5; N, 3.2.

Found: C, 46.8; H, 2.7; N, 3.55.

8-p-Toluidino-6-bromo-3-chlorojuglone. This was prepared by the same method as the previous compound. It crystallized from methyl ethyl ketone in dark violet elongated plates, which appear black in the mass, m.p. 251°; yield, 62%.

Anal. Calc'd for $C_{17}H_{11}BrClNO_2$: C, 52.0; H, 2.8; N, 3.6.

Found: C, 52.1; H, 3.0; N, 3.75.

8-Methoxy-3,6-dibromojuglone (VIII). (a) This was prepared by refluxing the sodium salt of 2,3,6-tribromojuglone with alcoholic methyl iodide as described by Wheeler and Andrews (8). The ether separated on cooling. The violet color disappeared much more rapidly than was reported by these workers, possibly because they failed to wash the sodium salt completely free from the sodium carbonate used in its preparation. If the experiment is stopped after two hours, and the solution concentrated to small bulk, the 2-ethoxy derivative separates on cooling; yield, 69%.

(b) A solution of 0.8 g. of the sodium salt of tribromojuglone in 100 cc. of methyl alcohol was boiled under reflux. The violet color rapidly disappeared and crystals began to separate from the solution in ten minutes. After boiling for thirty minutes the red suspension was cooled, and the product collected; yield, 66%.

(c) An ice-cold solution of 0.15 g. of 2-hydroxy-3,6-dibromojuglone in 75 cc. of ether was treated with an ether solution of diazome hane (from 0.5 g. of nitrosomethylurea). Orange crystals separated almost immediately, and after standing in the ice-bath for an hour, these were collected; yield, 66%.

(d) A solution of 0.25 g. of 2-ethoxy-3,6-dibromojuglone in 50 cc. of methyl alcohol containing a trace of sodium, was refluxed for nine hours. The methyl ether separated on cooling; yield, 52%.

All products were recrystallized from alcohol forming identical glistening orange needles, m.p. 211–212°. (Wheeler and Andrews record 209–210°.)

2-Ethoxy-3,6-dibromojuglone (VII). (a) This was prepared as for (VIII) (a) using alcoholic ethyl iodide, according to Wheeler and Andrews (8).

(b) The preparation of (VIII) (b) above was repeated using ethyl alcohol. Reaction was much slower, the solution only becoming red (by reflected light) after three hours. The solution was refluxed for five hours, and concentrated to small bulk. The ethyl ether separated on cooling; yield, 78%.

Both preparations afforded identical fine glistening orange needles, m.p. 139–141°, from alcohol. (Wheeler and Andrews report m.p. 134–136°.)

Further reactions of the sodium salt of 2,3,6-tribromojuglone. (a) A solution of 0.25 g. of the sodium salt in 15 cc. of water was refluxed for three hours. The blue-violet solution became red in one hour, and a brown precipitate appeared. The latter was collected, after cooling; 0.08 g., m.p. 170°. Recrystallization from glacial acetic acid afforded orange-red needles, m.p. 172°, identical with 2,3,6-tribromojuglone. The filtrate was acidified, and the orange precipitate collected; 0.1 g., m.p. 180–190°. After two crystallizations from glacial acetic acid the product formed orange needles, m.p. 206°, identical with 2-hydroxy-3,6-dibromojuglone. Repeating this experiment using 150 cc. of water gave approximately the same result.

(b) A suspension of 0.4 g. of the sodium salt in 6 cc. of dry methyl iodide was boiled under reflux for twelve hours. No visible change occurred, and all the sodium salt was recovered by evaporation of the methyl iodide.

(c) A solution of 0.2 g. of the sodium salt in 40 cc. of dry dioxane was refluxed with 0.2 cc. of methyl iodide for eight hours. There was no change in the blue-violet color and all the sodium salt was recovered on removal of the solvent.

SUMMARY

The constitution of a number of juglone derivatives, hitherto unknown or uncertain, has been determined. The structure of all known juglone compounds is now established.

ABERDEEN, SCOTLAND

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THE REACTION OF CHLOROSILANES WITH 2-METHOXYETHANOL
(METHYL CELLOSOLVE)

CHARLES A. BURKHARD

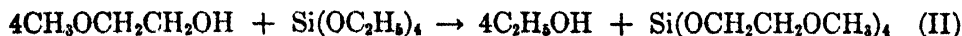
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In a recent paper by Abrahamson, Joffe, and Post (1), the reaction of 2-methoxyethanol with silicon tetrachloride was described. It is of interest to note that while *n*-butanol, *n*-pentanol, *n*-heptanol, and *n*-octanol form the corresponding orthosilicates (2), Abrahamson, *et al.* found that 2-methoxyethanol, even when present in excess, reacts with silicon tetrachloride to form only tris(2-methoxyethoxy)chlorosilane.



The introduction of an ether oxygen into an alcohol molecule would not be expected to exert such a pronounced steric effect, especially since the bulkier *n*-heptanol or *n*-octanol react under similar conditions to give *n*-heptyl and *n*-octyl orthosilicates.

Tetrakis(2-methoxyethoxy)silane was prepared by these authors (1), however, using alcohol interchange between ethyl orthosilicate and 2-methoxyethanol.



It is also of interest to note on examination of the reported physical data that the boiling points, indices of refraction, and densities for both tris(2-methoxyethoxy)chlorosilane and tetrakis(2-methoxyethoxy)silane are very nearly the same. From a consideration of estimated boiling points (3) and specific refractions (4) [R_D , Calc'd for tris(2-methoxyethoxy)chlorosilane, 0.2240, for tetrakis(2-methoxyethoxy)silane, 0.2339; Found 0.2352 and 0.2353 respectively], it appears as though the compound, which was reported as tris(2-methoxyethoxy)chlorosilane, is in reality tetrakis(2-methoxyethoxy)silane. On the other hand, data obtained from molecular weight determinations indicate that tris(2-methoxyethoxy)chlorosilane was obtained. Since no quantitative elemental analyses are given in support of either of these compounds, it was difficult to resolve this anomaly without repeating at least a portion of the preparative work.

Tetrakis(2-methoxyethoxy)silane was prepared in this Laboratory by reaction of 2-methoxyethanol with silicon tetrachloride in a molar ratio of 5:1. In addition, it was possible to prepare tris(2-methoxyethoxy)chlorosilane by reaction of 2-methoxyethanol with silicon tetrachloride in a molar ratio of 3:1. Tetrakis(2-methoxyethoxy)silane was formed in a considerable quantity even at this molar ratio (3:1).

Tetrakis(2-methoxyethoxy)silane was also obtained from the reaction of 2-

methoxyethanol with trichlorosilane in a molar ratio of 5:1. No tris(2-methoxyethoxy)chlorosilane or tris(2-methoxyethoxy)silane was obtained.

EXPERIMENTAL

Analytical Methods. Hydrolyzable chlorine was determined by titration of a weighed sample with standard sodium hydroxide solution. Silicon¹ was determined by hydrolyzing a weighed sample of the silicate with dilute hydrochloric acid in a quartz test tube. The quartz test tube had been previously conditioned by heating at 800° for one hour in a muffle furnace. After this heating, the tube was allowed to cool to room temperature in a desiccator. When cool, the test tube was wiped with a damp cloth and heated in a 100° oven for one hour, after which the tube was again cooled to room temperature in a desiccator and weighed. The hydrolysis was aided by carefully warming the test tube with an open flame. After the 2-methoxyethanol and the water were removed in this manner, the tube containing the resulting silicon dioxide was placed in the 800° muffle for one hour. The wiping and reheating procedure at 100° was again carried out after which the weight of silicon dioxide was obtained.

Apparatus and method. In the following experiments, the chlorosilane was placed in a three-necked flask, which was fitted with a dropping funnel, thermometer, and water-cooled condenser. A dry-ice cold-finger condenser was placed on the top of the water-cooled condenser. The 2-methoxyethanol was added dropwise. When the alcohol had been added, the reaction mixture was heated until the evolution of hydrogen chloride ceased. The products were then distilled under *vacuo*.

Tetrakis(2-methoxyethoxy)silane. The procedure used to prepare tris(2-methoxyethoxy)chlorosilane by Abrahamson, *et al.* (1) was repeated, using 150 cc. of 2-methoxyethanol and 44 cc. of silicon tetrachloride (*ca.* 5:1 molar ratio). Distillation of the reaction product gave, in addition to unreacted 2-methoxyethanol, 94.9 g. of tetrakis(2-methoxyethoxy)silane (76% yield); b.p. 179–182° (10 mm.) n_D^{20} 1.4219, d_4^{20} 1.0789. This silane is water-soluble. No chlorine-containing products were obtained.

Anal. Calc'd for $C_{12}H_{28}O_8Si$: Si, 8.54; R_D = 0.2339; MR_D = 76.8.

Found: Si, 8.5, 8.5; R_D = 0.2355; MR_D = 77.3

Tris(2-methoxyethoxy)chlorosilane. Three moles (228 g.) of 2-methoxyethanol and one mole (170 g.) of silicon tetrachloride were allowed to react. Distillation of the reaction product gave in addition to a small amount of a low-boiling unidentified chlorine-containing material, 50 g. of tris(2-methoxyethoxy)chlorosilane (18% yield), 65 g. of less pure tris(2-methoxyethoxy)chlorosilane, and 50 g. of tetrakis(2-methoxyethoxy)silane; b.p. 159–162° (10 mm.), n_D^{20} 1.4238, d_4^{20} 1.1225. This chlorosilane is water-soluble.

Anal. Calc'd for $C_6H_{11}ClO_3Si$: Si, 9.72; Cl, 12.28; R_D = 0.2241; MR_D = 64.7.

Found: Si, 9.6, 9.6; Cl, 12.4, 12.1, 12.0; R_D = 0.2272; MR_D = 65.6..

Reaction of trichlorosilane and 2-methoxyethanol. One mole (135.5 g.) of trichlorosilane and five moles (380 g.) of 2-methoxyethanol were allowed to react. Distillation of the reaction product gave in addition to unreacted 2-methoxyethanol 231 g. of a halogen-free liquid boiling at 177–180° (10 mm.) n_D^{20} 1.4221, which was shown to be tetrakis(2-methoxyethoxy)silane (70% yield).

SUMMARY

1. Tris(2-methoxyethoxy)chlorosilane and tetrakis(2-methoxyethoxy)silane have been prepared from silicon tetrachloride and 2-methoxyethanol and have been definitely characterized.

¹ The procedure for the determination of silicon in organosilicates was suggested by Dr. E. W. Balis.

2. Tetrakis(2-methoxyethoxy)silane results from the reaction of trichlorosilane with excess 2-methoxyethanol.

SCHENECTADY 5, N. Y.

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FACTORS INFLUENCING POLYSULFONE FORMATION. II. A NEW METHOD OF INDUCTION WITH CONTROL OF POLYMER LENGTH

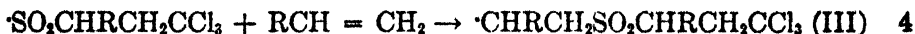
M. S. KHARASCH AND H. N. FRIEDLANDER

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In a previous paper (1) it has been shown that a mixture of ascaridole and hydrogen bromide is effective in inducing the heteropolymerization of sulfur dioxide and olefins, which ordinarily gives poor yields of polysulfones. Many other polymerizing agents of varying efficacy are known (2). The most efficient of these are those generally recognized as producing free radicals in solution, namely, light, oxygen, and peroxidic materials. With none of the agents previously studied can the length of the polymer chain be controlled, the products being polymers of the molecular weight range of 50,000 to 200,000.

It has been shown in this laboratory (3) that bromotrichloromethane is dissociated by light into bromine atoms and free trichloromethyl radicals which can initiate free-radical chain reactions. We have found that bromotrichloromethane when irradiated by light can initiate the copolymerization of sulfur dioxide and olefins. The length of the polymer chain depends on the ratio between the concentrations of bromotrichloromethane and sulfur dioxide. By variation of this ratio the nature and length of the polymer chain can be controlled.

The reactions involved may be formulated as follows:



Bromotrichloromethane and sulfur dioxide compete with each other in reactions 3a and 3b, 5a and 5b for the free radicals I and III. Radical V can react, as did radical III in reactions 5b and 6, with sulfur dioxide and the olefin to yield higher polymerized material, or it can react with bromotrichloromethane, as in reaction 5a, to yield a polysulfone. Therefore, the polysulfone molecules produced from this bromotrichloromethane-induced polymerization of sulfur dioxide and

an olefin contain n molecules of sulfur dioxide, $n + 1$ molecules of olefin, and one molecule of bromotrichloromethane. Furthermore, the average molecular weight of the polymer is determined by the ratio of sulfur dioxide to bromotrichloromethane in the competing reactions 3a vs. 3b, 5a vs. 5b, etc.

Table I illustrates the control of polymer size for the reaction of 1-octene with sulfur dioxide by varying the ratio of sulfur dioxide to bromotrichloromethane. Since the polymers contain both sulfur and halogen it is possible to calculate the average value of n from the silver equivalent and the per cent of sulfur in the compound utilizing the equation $n = \text{Ag Equiv.} \times \%S/801.5$.¹

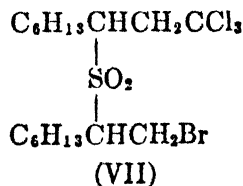
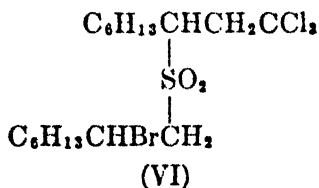
From experiments made with equimolar quantities of bromotrichloromethane and sulfur dioxide with 1-octene, a viscous oil is obtained by molecular distillation. The oil is 1,1,1-trichloro-3-nonyl 2-bromooctyl sulfone (VI), whose structure is in accord with the reaction scheme outlined.² This product definitely has

TABLE I
CONTROL OF POLYMER SIZE IN 1-OCTENE POLYSULFONE FORMATION

RUN	RATIO BrCCl ₃ /SO ₂	NATURE OF THE POLYMER	%S	Ag EQUIV.	MOL. WT.*	\bar{n}
2	2/5	Viscous oil	6.96	122.2	500	1.0
3	1/6	Sticky, taffy-like glass	14.36	295.7	1200	5.3
4	1/10	Pliable solid	16.10	478	1900	9.6
6	1/65	Brittle solid	18.94	2374	11,000	68

* Four times Ag Equiv.

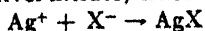
not the head-to-head, tail-to-tail structure (VII) analogous to that suggested by the studies of Marvel and co-workers (4) on propylene and pentene polysulfones.



EXPERIMENTAL

Polysulfone formation induced by bromotrichloromethane. Method one. A quarter of a mole of olefin and the desired amount (from 0.01 to 0.1 mole) of bromotrichloromethane were placed in a Pyrex tube and degassed on a vacuum line. The desired amount of sulfur dioxide (0.3 to 0.8 mole) was condensed into the tube which was then sealed. The sealed tube was shaken between two 100-watt Mazda lamps placed one foot from the tube. After several days of radiation the tube was opened, and the excess sulfur dioxide and olefin were distilled. Any small quantity of olefin-bromotrichloromethane addition product (such as 1,1,1-trichloro-3-bromononane obtained from 1-octene) was removed by heating the

¹ The term Ag equiv. is defined as the number of grams of the halogen-containing compound which react with one mole of silver nitrate, in accordance with the reaction:



² Details of proof of structure are presented in the Experimental Part.

reaction mixture to 50° at 10^{-6} mm. In the cases of nearly equal molar ratios of bromotrichloromethane to sulfur dioxide, the tube contents were subjected to molecular distillation. The results obtained by this method are recorded in Table II.

Method two. Bromotrichloromethane (1.1 mole, 220 g.) and 1-octene (1.3 mole, 150 g.) were placed in a tube internally illuminated by a mercury vapor-neon fluorescent coil and sulfur dioxide was bubbled into the solution through a sintered-glass gas disperser. By this method 180 g. of 1,1,1-trichloro-3-bromononane, 50 g. of 1,1,1-trichloro-3-nonyl 2-bromooctyl sulfone (VII), and 50 g. of higher-molecular-weight polysulfones were obtained in eleven hours.

Identification of heavy oil obtained by molecular distillation from the reaction of 1-octene and sulfur dioxide in the presence of bromotrichloromethane (1,1,1-trichloro-3-nonyl 2-bromooctyl sulfone). Subjection of the reaction product of 1-octene with nearly equal quantities of sulfur dioxide and bromotrichloromethane to molecular distillation yielded a heavy oil, n_D^{20} 1.5028. The heavy oil does not react with cold alcoholic silver nitrate and thus does not contain any SO_2Br groups.

TABLE II
RESULTS OF REACTIONS BY METHOD ONE

RUN	OLEFIN (MOLE)	$BrCCl_3$ (MOLE)	SO_2 (MOLE)	RATIO $BrCCl_3/SO_2$	WT. ADDUCT (G.)	WT. POLY- MERS (G.)	%S	Ag EQUIV.	n^a
2	C_8H_{16} , 0.25	0.12	0.31	2/5	18 ^a	2) ^d 16	6.96 15.23	122.2 342.2	1.0 6.5
3	C_8H_{16} , 0.25	0.12	0.78	1/6	2 ^a	50	14.36	295.7	5.3
4	C_8H_{16} , 0.25	0.06	0.60	1/10	4 ^a	60	16.10	478	9.6
6	C_8H_{16} , 0.25	0.012	0.78	1/65	1.5 ^a	40	18.94	2874	68
7	C_8H_7Cl , 0.25	0.12	0.60	1/5	3 ^b	7	11.19	79.6	2

^a 1,1,1-Trichloro-3-bromononane.

^b 1,1,1,4-Tetrachloro-3-bromobutane.

^c For octene $n = \%S \times Ag\ Equiv./801.5$; for allyl chloride $n = 5 \times \%S \times Ag\ Equiv./3206 - \%S \times Ag\ Equiv.$

^d The 2-gram fraction was removed from the 16-gram fraction by molecular distillation. This 2-g. fraction corresponds to an adduct of one mole of bromotrichloromethane to one mole of sulfur dioxide to two moles of 1-octene.

Anal. Calc'd for $C_{17}H_{32}BrCl_3O_2S$: S, 6.60; Ag Equiv., 121.7; Mol. Wt., 486.6.

Found: S, 6.96, 7.23, 7.07; Ag Equiv., 122.5, 122.2, 125.5; Mol. Wt., (by f.p. lowering of benzene) 500.5, 500.0.

The heavy oil can be titrated in alcoholic solution with cold alcoholic KOH. One molecule of hydrogen bromide is lost and an olefin is obtained.

Anal. Calc'd for $C_{17}H_{31}Cl_3O_2S$: S, 7.92; Ag Equiv., 135.2.

Found: S, 7.89; Ag Equiv., 134.3.

The olefin was subjected to ozonization in ethyl acetate solution at -60°. The ethyl acetate was evaporated at reduced pressure, and the resulting ozonide decomposed with water. The mixture was extracted with ether. The ether extract was washed with aqueous sodium carbonate and steam-distilled. The residue from the steam distillation contained sulfur and chlorine. The steam distillate yielded a red-orange 2,4-dinitrophenylhydrazone, which melted at 125-126°. This hydrazone proved to be identical with that obtained on refluxing an authentic sample of hexaldehyde with hydrochloric acid and treating the product with 2,4-dinitrophenylhydrazine. The authentic 2,4-dinitrophenylhydrazone of the dehydrated aldol of hexaldehyde melted at 126-127°, and its melting point was not depressed by admixture with the hydrazone of the aldol obtained from ozonization.

Anal. Calc'd for $C_{11}H_{24}N_4O_4$: C, 59.8; H, 7.2; N, 15.5.

Found: C, 61.3; H, 6.8; N, 15.6.

A careful search for formaldehyde in the water-soluble fractions and in the ethyl acetate from the ozonization proved fruitless.

SUMMARY

A new method for the induction of the heteropolymerization of sulfur dioxide and olefins by means of bromotrichloromethane and light is described, and the mechanism of reaction is discussed.

The control of polymer molecular weight by varying the relative concentrations of bromotrichloromethane and sulfur dioxide is demonstrated.

The simplest one-link polymer of sulfur dioxide and 1-octene formed in the presence of bromotrichloromethane is shown to be 1,1,1-trichloro-3-nonyl 2-bromooctyl sulfone.

CHICAGO 37, ILL.

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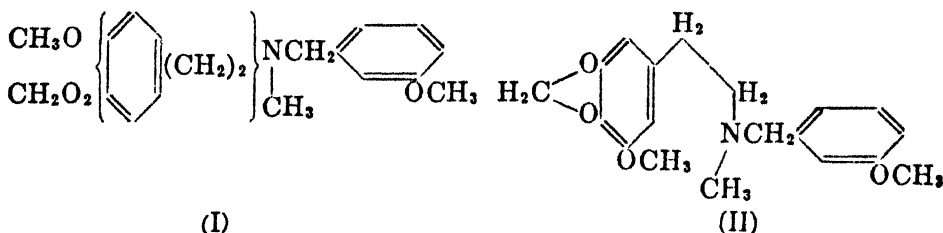
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SYNTHESIS OF CERTAIN COMPOUNDS RELATED TO α -FAGARINE¹

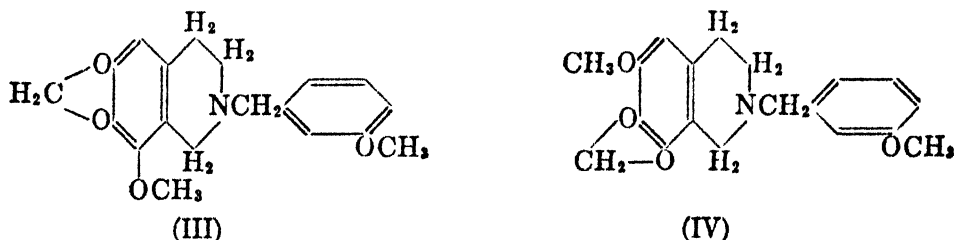
C. ERNST REDEMANN, BURNETT B. WISEGARVER, AND ROLAND N. ICKE

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Deulofeu and co-workers (1, 2, 3) have proposed (I) as a provisional structure for α -fagarine, the position of the methoxyl, methylenedioxy, and methylene groups being unestablished. Because α -fagarine has been reported as effective in arresting cardiac arrhythmias (1), especially in some cases where quinidine had failed, it was of interest to synthesize one of the possible compounds of the general structure (I) in order to compare its chemical and pharmacological properties with those of α -fagarine.



The distribution of the methoxyl, methylenedioxy, and methylene groups selected in (II) was that considered most probable, namely the 3,4-methylenedioxy-5-methoxyphenethylamine arrangement. This was thought to be the most probable arrangement since it is that found in numerous alkaloids, *e.g.* cotarnine, gnoscopine, narceine, narcotine, and many others. For comparison of their chemical and pharmacological properties with that of the open-chain compound (II) there were also prepared the tetrahydroisoquinolines (III) and (IV).



For the synthesis of (II), *N*-(*m*-methoxybenzyl)homomyristiclyamine was first synthesized by catalytic reduction of the Schiff base from *m*-methoxybenzaldehyde and homomyristiclyamine. The resulting secondary amine was then methylated with methyl sulfate to give the desired tertiary *N*-methyl amine (II). The required homomyristiclyamine has previously been prepared

¹ Surry [*J. Am. Chem. Soc.*, **70**, 2887 (1948)] reported the synthesis of *N*-(3-methoxybenzyl)-*N*-methyl-3-methoxy-4,5-methylenedioxyphenethylamine after the present manuscript had been submitted for publication. Our conclusions support their findings.

by several methods (8, 10, 11, 12, 13), but it was thought that the facile rhodanine synthesis of Gränacher (4, 5) might be used to advantage in the synthesis of the amine from myristicinaldehyde. Homomyristicylamine was prepared from myristicinaldehyde in an over-all yield of 51% using this method.

The tetrahydroisoquinolines (III) and (IV) were prepared from N-(*m*-methoxybenzyl)homomyristicylamine by ring closure with formaldehyde and hydrochloric acid following the method of Späth (6). While only one tetrahydroisoquinoline was possible with the compound of Späth, two are possible here and both were obtained. These were separated by the difference in solubility of their hydrochlorides. Too little material was available to determine the absolute position of the methoxyl and methylenedioxy groups in these two isoquinolines. However, upon the basis of the work of Salway (14) on the synthesis of cotarnine in which corresponding 1-benzyltetrahydroisoquinolines were synthesized and identified, the structures tentatively assigned are 2-(*m*-methoxybenzyl)-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (III) for the isomer having the higher-melting hydrochloride and 2-(*m*-methoxybenzyl)-6-methoxy-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (IV) for the isomer having the lower-melting hydrochloride. Further work is needed to establish these structures with certainty.

α -Fagarine is reported (2) to melt at 169–170°, its hydrochloride melts at 192° and the base gives a red-violet color with concentrated sulfuric acid which changes to purple and finally, upon long standing, to a dark brown. The N-methyl-N-(*m*-methoxybenzyl)homomyristicylamine (II) is a liquid which could not be crystallized, its hydrochloride melts at 165–167° and with concentrated sulfuric acid it gives a clear yellow color which becomes green-yellow on standing. Both of the tetrahydroisoquinolines give a yellow color with sulfuric acid, showing they too differ from α -fagarine. Hence it may be concluded that none of these substances is identical with α -fagarine.

The data on the pharmacological trial of these compounds in our laboratories will be published elsewhere by Gordon A. Alles and Charles H. Ellis.

Acknowledgment. The authors wish to express their appreciation to Dr. Gordon A. Alles for suggesting this work and for his helpful criticism during its progress and in the preparation of the manuscript.

EXPERIMENTAL

All melting points are uncorrected.

Myristicinaldehyde. Fractional distillation of 700 g. of Dodge and Olcott heavy nutmeg oil gave 436 g. of myristicin, b.p. 152–155°/18 mm. This was isomerized to isomyristicin by boiling under reflux for 24 hrs. with 1.4 l. of 3 *N* ethanolic potassium hydroxide. From this mixture was isolated 352 g. of isomyristicin, b.p. 162–163°/15 mm., which after recrystallization from methanol gave isomyristicin as white needle-crystals, m.p. 43–44°; Power (7) gives 44°. The isomyristicin was oxidized in 96-g. batches according to Salway (8). The aldehyde was obtained as a white crystalline powder, m.p. 131–132°, in 41% yield. The aldehyde gave a 2,4-dinitrophenylhydrazone, dark brown red needles, m.p. 232°, identical with that described by Baker (9).

5-Myristicinalrhodanine. A mixture of 118 g. of myristicinaldehyde, 90 g. of rhodanine,

165 g. of anhydrous sodium acetate, and 500 ml. of glacial acetic acid was gently boiled for 1 hr. After cooling, the mixture was poured into 5 l. of cold water. The orange-yellow solid was washed with alcohol and ether, and dried; yield 165 g. (85%). A sample recrystallized from "Cellosolve" melted at 254–255°.

Anal. Calc'd for $C_{12}H_9NO_4S_2$: C, 48.80; H, 3.07.

Found: C, 48.95; H, 3.10.

α -Thiono- β -(3,4-methylenedioxy-5-methoxyphenyl) propionic acid. A suspension of 104 g. of myristicin alrhodanine in 420 ml. of 4 *N* sodium hydroxide was heated with stirring in a boiling water-bath until practically all the solid had dissolved. The filtered solution was cooled to 10° and 420 ml. of an ice-cold solution of 4 *N* hydrochloric acid was rapidly added with vigorous stirring. The thiono acid separated as a granular yellow solid. The yield was nearly theoretical, but it proved to be wise to use this product directly in the following step without drying or further purification.

A sample was recrystallized from aqueous methanol for analysis; yellow crystalline powder, m.p. 153–154° dec.

Anal. Calc'd for $C_{11}H_{10}O_5S$: C, 51.96; H, 3.97.

Found: C, 51.4; H, 4.14.

α -Oximino- β -(3,4-methylenedioxy-5-methoxyphenyl) propionic acid. The thiono acid from 165 g. of myristicin alrhodanine was dissolved in a solution prepared by dissolving 38.5 g. sodium in 1100 ml. of ethanol and adding a solution of 115 g. of hydroxylammonium chloride in 100 ml. of water. This solution was heated to boiling for 30 minutes, filtered to remove sodium chloride and any insoluble material, and evaporated to dryness under reduced pressure. The residue was dissolved in dilute sodium hydroxide, filtered, and well cooled, after which it was made acid to Congo Red while stirring with a mechanical stirrer. The crystalline product was filtered off, washed with water, and dried; weight 131 g. (93% yield, based upon the myristicin alrhodanine, 2 steps).

A sample was recrystallized from 20% methanol-water for analysis; microscopic, colorless needles, m.p. 150–151°.

Anal. Calc'd for $C_{11}H_{11}NO_4$: C, 52.2; H, 4.38.

Found: C, 52.17; H, 4.62.

3,4-Methylenedioxy-5-methoxyphenylacetonitrile. To 400 ml. of acetic anhydride at 45° was added, in small portions, 131 g. of the oximino acid. The spontaneous reaction caused the temperature to rise to 90°, with the evolution of carbon dioxide. After boiling for 10 min. the solution was evaporated to dryness under reduced pressure, the cooled residue was taken up in benzene, washed with water and then dilute sodium hydroxide, dried over magnesium sulfate, and distilled under reduced pressure. The fraction boiling at 160–165°/2 mm. weighed 68.5 g. (70% yield). After recrystallizing from methanol a product melting at 89–90° was obtained. Hahn (13) gives m.p. 90°.

Homomyristicylamine. A mixture of 36.2 g. of 3,4-methylenedioxy-5-methoxyphenylacetonitrile, 100 ml. of methanol, 200 ml. of a saturated solution of ammonia in methanol, and 4 ml. of Raney nickel catalyst sludge was reduced at 100° for 2 hrs. at an initial pressure of 420 lbs./sq. in. The catalyst was filtered off, the ammonia and methanol distilled, and then the residue, giving 33.6 g., b.p. 145–147°/3 mm. (91% yield). The hydrochloride melted at 163–164° in agreement with Decker and Becker (10).

*N-(*m*-methoxybenzyl)homomyristicylamine hydrochloride.* A mixture of 9.8 g. of homomyristicylamine and 6.8 g. of *m*-methoxybenzaldehyde was allowed to stand for 10 min., during which time it became warm and turbid from the separation of water. The mixture was then dissolved in 50 ml. of ethanol, 100 mg. of Adams platonic oxide catalyst was added followed by hydrogenation at 3 atmospheres pressure for 2 hrs. at ambient temperature. The catalyst was removed and the solution was acidified with ethanolic hydrogen chloride. The amine hydrochloride crystallized out. Upon reworking the filtrate, additional amine salt was isolated; in all, 12.7 g. (72% yield) of crystalline salt, m.p. 142–143° was obtained.

Anal. Calc'd for $C_{14}H_{21}NO_4 \cdot HCl$: C, 61.44; H, 6.30; Cl, 10.08.

Found: C, 61.80; H, 6.32; Cl, 10.02.

N-methyl-N-(m-methoxybenzyl)homomyristicylamine. A solution of 6.5 g. of *N*-(*m*-methoxybenzyl)homomyristicylamine, obtained from the hydrochloride by treatment with alkali, in 50 ml. of ethyl ether was treated with 2.6 g. of methyl sulfate. The solution was refluxed for 5 min., water was added, the solution made strongly basic with sodium hydroxide, and the ether and aqueous phases were separated. The ether phase was treated with 4 *N* hydrochloric acid and sodium nitrite to convert any secondary amine into the nitroso derivative, insoluble in dilute acid. The ether layer was discarded and the aqueous layer was made basic with sodium hydroxide. The amine which separated was extracted with ether and the ether layer was dried over potassium carbonate. After removing the drying agent, the ether was distilled leaving a thick oily residue (3.3 g.) which would not crystallize.

The base was dissolved in ethanol, treated with a slight excess of ethanolic hydrogen chloride, ether was added just to turbidity, and the solution was cooled in the refrigerator, giving 3.4 g. of white crystals which after recrystallizing from ethanol-ether melted at 165–167°.

Anal. Calc'd for $C_{19}H_{21}NO_4 \cdot HCl$: C, 62.37; H, 6.61; Cl, 9.69; N, 3.83.

Found: C, 62.58; H, 6.74; Cl, 9.68; N, 3.84.

Cyclization of N-(m-methoxybenzyl)homomyristicylamine. A mixture of 11.5 g. of *N*-(*m*-methoxybenzyl)homomyristicylamine, 5 ml. of 40% formaldehyde, and 10 ml. of water was heated for 30 min. on a boiling water-bath. The aqueous layer was decanted from the gummy material and the latter was warmed with 150 ml. of 2 *N* hydrochloric acid. After adding 30 ml. of ethanol the solution was allowed to cool. The crystals which separated were washed with ethanol, the ethanol washings being kept separate from the aqueous filtrate; 1.8 g. of crystals, m.p. 115°, was obtained. From the aqueous filtrate 1.8 g. of crystals, m.p. 190–192°, separated upon prolonged standing. By reworking the filtrate a total of 2.8 g. of the higher-melting fraction was obtained. The lower-melting isomer was obtained from the filtrate by a procedure described below.

2-(m-Methoxybenzyl)-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (III). The free isoquinoline obtained from 3.8 g. of the higher-melting hydrochloride was heated for 30 min. with 3 ml. of acetic anhydride. The excess acetic anhydride was destroyed with water, the solution was acidified with an excess of 1 *N* hydrochloric acid and the non-basic organic material was extracted with ether and discarded. The aqueous layer was evaporated to dryness and the residue was crystallized from ethanol-ether; weight 3.0 g., m.p. 189–191°.

Anal. Calc'd for $C_{19}H_{21}NO_4 \cdot HCl$: C, 62.71; H, 6.10; Cl, 9.73.

Found: C, 62.84; H, 6.10; Cl, 9.62.

2-(m-Methoxybenzyl)-6-methoxy-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (IV). The base from the combined aqueous filtrates of several cyclizations was liberated with sodium hydroxide, extracted with ether, dried, and the ether evaporated. The residue was heated on a boiling water-bath for 30 min. with an excess of acetic anhydride, the excess anhydride was destroyed with water, the solution was cooled and acidified with 50 ml. of 1 *N* hydrochloric acid. The solution was evaporated to dryness and the residue was crystallized from ethanol-ether, giving 2.7 g. of material melting at 120–125°. Recrystallization from ethanol-ether failed to change the melting point.

Anal. Calc'd for $C_{19}H_{21}NO_4 \cdot HCl$: C, 62.71; H, 6.10; Cl, 9.73.

Found: C, 62.0, 62.0; H, 5.92, 6.17; Cl, 9.76.

SUMMARY

N-(*m*-methoxybenzyl)-*N*-methylhomomyristicylamine and its hydrochloride have been synthesized as one of the possible structures for α -fagarine. Likewise the two isomeric 1,2,3,4-tetrahydroisoquinolines, 2-(*m*-methoxybenzyl)-6,7-methylenedioxy-7-methoxy- and 2-(*m*-methoxybenzyl)-6-methoxy-7,8-methyl-

enedioxy-, were prepared and compared with α -fagarine. None of these structures is identical with α -fagarine.

PASADENA, CALIFORNIA

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2,3-DIMETHOXY-6-NITRO-9-(γ -DIETHYLAMINO- β -
HYDROXYPROPYLAMINO)ACRIDINE¹

CHARLES S. MILLER AND CHARLOTTE A. WAGNER

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The nitroacridine V,¹ 2,3-dimethoxy-6-nitro-9-(γ -diethylamino- β -hydroxypropylamino)acridine, was reported by German investigators (1) to exhibit chemotherapeutic activity in experimental and clinical typhus infections. The results of later work in this country show that this compound has a beneficial effect in both experimental rickettsial (2) and viral infections (3). These findings make this compound desirable as a standard drug in comparative testing programs.

Although the steps in the synthesis of V have been outlined (1), no detailed description of its preparation or physical properties has been published.² Attempts in this laboratory to carry out the outlined synthesis under conditions that are described in the chemical literature for similar acridine compounds were unsuccessful. A satisfactory laboratory procedure is described in this paper. The compound thus obtained was identical with the German material.³

When the Ullman reaction between 2-chloro-4-nitrobenzoic acid (I) and 4-aminoveratrole (II) was carried out in *n*-amyl alcohol at 140° or in nitrobenzene at 140° according to usual procedures, only dehalogenation of the 2-chloro-4-nitrobenzoic acid to 4-nitrobenzoic acid resulted. No 2-(3,4-dimethoxyphenylamino)benzoic acid, (III) was obtained. This result is similar to that observed by Goldberg and Kelly (4) with this chloronitrobenzoic acid and *p*-phenylenediamine in the Ullman reaction. These workers found, however, that the desired 2-(4-aminophenylamino)-4-nitrobenzoic acid was obtained in isopropyl alcohol at 80°. Albert and Gledhill (5) obtained 2-(4-ethoxyphenylamino)-4-nitrobenzoic acid in good yield from the Ullman reaction between 2-chloro-4-nitrobenzoic acid and *p*-phenetidine in boiling *n*-butyl alcohol. Using these conditions in our laboratory, the reaction of I and aminoveratrole (II) was unsuccessful; in isopropyl alcohol at 80° no reaction occurred. Yields of III up to 34% were obtained, however, when *n*-amyl alcohol was employed and the temperature carefully regulated between 95–100°. The substitution of copper acetate or copper sulfate for the copper powder led to lower yields of III. In all cases where the temperature was high enough to bring about reaction some dehalogenation occurred and *p*-nitrobenzoic acid resulted.

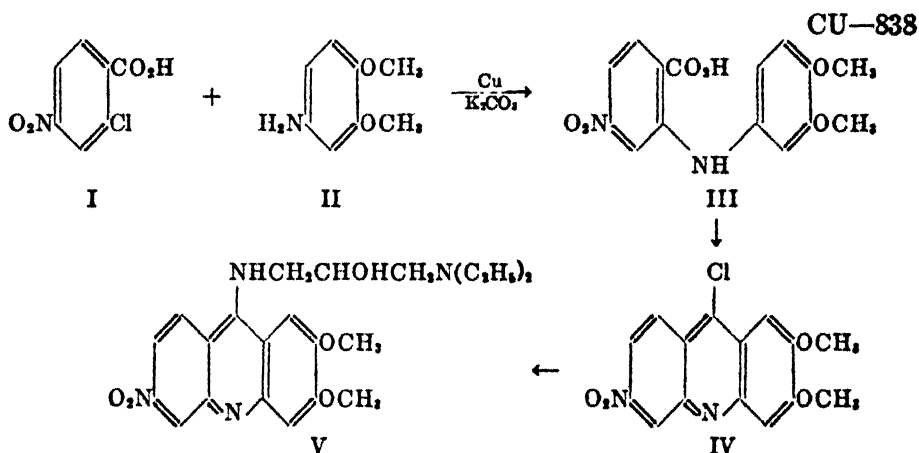
¹ This compound has been designated "nitroakridin 3582" in the report of the German work (1) and in reports in this country (2, 3).

² Water-soluble, neutral salts have been reported in the patent literature, German Patent 632,733 (1936); U. S. Patent 2,092,114 (1937) and reference is made to uses of the compound, Eisleb, *cf. Chem. Abstr.*, **31**, 5802 (1937), Keller, *cf.*, *Chem. Abstr.*, **36**, 6688 (1942).

³ We are indebted to Dr. J. E. Smadel, of the Army Medical School, who supplied a sample of the German material to Dr. Bettylee Hampil of the Department of Virus Research of these laboratories.

The preparation of III through the Ullman reaction of 2-amino-4-nitrobenzoic acid (9) and 4-iodoveratrole (11) was unsuccessful. Also, the reaction of I and 4-acetylaminoveratrole (12) was unpromising; a small amount of an uncharacterized product resulted.

The direct cyclization of III to the 9-chloroacridine IV, proceeded smoothly (yield, 70%) using phosphoryl chloride according to the procedure of Magidson and Grigorowsky (6). The German synthesis (1) of IV apparently involved the intermediate 9-acridone which was then converted to the 9-chloroacridine. The reaction of γ -diethylamino- β -hydroxypropylamine with IV in phenol by the method of Magidson and Grigorowsky (7) gave a 67% yield of V.



EXPERIMENTAL PART^{4, 5}

The 2-chloro-4-nitrobenzoic acid I, was prepared by procedures in the literature (9); *o*-toluidine \rightarrow 2-amino-4-nitrotoluene (77%) (8) [or *p*-nitrotoluene (13)] \rightarrow 2-chloro-4-nitrotoluene (64%) (9) \rightarrow I (42%) (6). 4-Aminoveratrole (II) was obtained by the method of Clark (10); veratrole \rightarrow 4-nitroveratrole (96%) \rightarrow II (54%).

2-(3,4-Dimethoxyphenylamino)-4-nitrobenzoic acid (III). A mixture of 340 cc. of distilled *n*-amyl alcohol, 25 g. (0.124 mole) of 2-chloro-4-nitrobenzoic acid and 25 g. of anhydrous potassium carbonate was placed in a 1-liter, three-necked flask that was fitted with a stainless steel leaf stirrer and a "Glascol" heater. A small quantity of the alcohol was allowed to distill to remove any water present. The potassium salt of the acid formed a flocculent precipitate during this process. The mixture was cooled to 95° and 31.8 g. (0.21 mole) of aminoveratrole and 0.75 g. of copper powder added. This mixture was heated with good stirring at 95–100° for ten hours. After standing overnight the reaction mixture was added to 500 cc. of ether and filtered. The solid was washed by resuspension in ether, the mixture filtered, and the solid washed on the filter with ether. The dark solid was extracted three times with boiling water (total volume, 1 liter) and the insoluble material discarded. The extract was treated with charcoal. The filtrate from the charcoal was heated to boiling and made just acid to Congo Red by the dropwise addition of dilute hydrochloric acid. The yellow-orange solid that separated was removed immediately from the boiling solution and washed with hot water and dried, yield, 13.66 g., (34.3%), m.p. 222–224°. A sam-

⁴ All melting points are uncorrected for stem exposure.

⁵ All analyses were performed by Mr. K. B. Streeter, and the Misses Ruth M. Lynch and Thelma V. Plank, of these laboratories.

ple was purified by repeated recrystallization from 50% alcohol and from acetic acid and water, m.p. 227.5–228°.

Anal. Calc'd for $C_{15}H_{11}N_2O_6$: C, 56.61; H, 4.43; N, 8.80; CH_3O , 19.50.

Found: C, 55.78; H, 4.64; N, 8.71; CH_3O , 18.73.

On cooling and further acidification of the aqueous extract, additional solid separated. This consisted principally of *p*-nitrobenzoic acid.

2,3-Dimethoxy-6-nitro-9-chloroacridine (IV). A mixture of 12 g. (0.036 mole) of 2-(3,4-dimethoxyphenylamino)-4-nitrobenzoic acid and 120 cc. of freshly distilled phosphoryl chloride was refluxed gently for 2.5 hours. The excess phosphoryl chloride was removed under reduced pressure while heating in a warm water-bath. The residue was treated with crushed ice and the resulting yellow solid was removed, washed with water, then suspended in dilute aqueous sodium bicarbonate solution and the suspension stirred until effervescence ceased. The mixture was filtered and the solid washed with water and dried. The product was recrystallized from 225 cc. of hot reagent pyridine, yield, 8.14 g. (70.7%), m.p. 252–253° dec. The melting point is not exactly reproducible and depends upon the rate of heating.

Anal. Calc'd for $C_{15}H_{11}ClN_2O_4$: C, 56.54; H, 3.48; N, 8.79; CH_3O , 19.48.

Found: C, 56.24; H, 3.40; N, 8.76; CH_3O , 19.49.

2,3-Dimethoxy-6-nitro-9-(γ -diethylamino- β -hydroxypropylamino)acridine (V). A mixture of 21.41 g. (0.067 mole) of 2,3-dimethoxy-6-nitro-9-chloroacridine and 63 g. of phenol was heated in an oil-bath carefully regulated between 85–90° until the solid dissolved. With the temperature maintained at 85–90°, 23 g. (0.158 mole) of γ -diethylamino- β -hydroxypropylamine* was added dropwise over a 25-minute period with constant manual stirring. Heating was continued at this temperature with occasional manual stirring for 1.5 hours. A precipitate formed during the addition of the amine but dissolved during one hour. The mixture was cooled and twice its volume of commercial anhydrous alcohol added. This solution was made acid to Congo Red by dropwise addition of concentrated hydrochloric acid. Slightly more than two volumes of ether was added with stirring and the liquid decanted immediately from the oily solid that separated. The solid was washed several times with ether and then dissolved in 1.5 liters of water. To this solution 1.5 liters of alcohol was added and a small quantity of insoluble residue removed and discarded. The filtrate was made basic by the addition of dilute ammonium hydroxide and diluted slowly with three liters of water. After complete precipitation, the red solid was removed, washed with water, and dried, yield, 20.14 g. (67%), m.p. 103°; (the melt resolidified and melted again over a range). A small sample of this material was further purified by suspending in water and adding dilute hydrochloric acid until acid to Congo Red. The solution was diluted with alcohol, treated with charcoal and the product precipitated by addition of ammonia, m.p. 109–115°. This material was found to contain 4.05% water on drying at 100° under vacuum and over phosphorus pentoxide. (Theory for one mole of water 4.04%.) This material was identical with the base recovered from a sample of the German dihydrochloride by treatment of an aqueous solution with dilute ammonium hydroxide.

The anhydrous base was obtained by crystallization from 200 cc. of boiling acetone, 14.8 g., m.p. 166–167°. After recrystallization, the melting point was 168–169°.

Anal. Calc'd for $C_{22}H_{28}N_4O_4$: C, 61.66; H, 6.59; N, 13.08; CH_3O , 14.48.

Found: C, 61.77; H, 6.72; N, 12.83; CH_3O , 14.45.

This material was reconverted to the low-melting hydrate by precipitation from an aqueous acid solution by ammonia.

The dihydrochloride was prepared as follows: The anhydrous base was suspended in the minimum volume of water and dilute hydrochloric acid added until acid to Congo Red. The solution was diluted with a large volume of acetone and allowed to stand for sixteen hours. The yellow solid was removed, washed with acetone and dried at room temperature,

* The γ -diethylamino- β -hydroxypropylamine was produced by the Sharples Chemical Corporation and kindly supplied by Dr. R. C. Elderfield of Columbia University.

m.p. 219–220° dec. On drying at 100° (2 mm.) over phosphorus pentoxide it changed from yellow to orange and lost weight corresponding to a dihydrate. (H_2O Calc'd 6.70%. Found 6.82%).

Anal. Calc'd for $C_{21}H_{23}N_3O_6 \cdot 2HCl$: N, 11.17; CH_2O , 12.38.

Found: N, 11.10; CH_2O , 12.39.

SUMMARY

The synthesis of 2,3-dimethoxy-6-nitro-9-(γ -diethylamino- β -hydroxypropyl-amino)acridine in satisfactory yield is described.

GLENOLDEN, PA.

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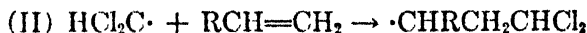
REACTIONS OF ATOMS AND FREE RADICALS IN SOLUTION. XV. THE ADDITIONS OF BROMODICHLOROMETHANE AND DIBROMODICHLOROMETHANE TO OLEFINS. THE PREPARATION OF 2-ALKENALS

M. S. KHARASCH, B. M. KUDERNA, AND W. URRY

Further investigation of the peroxide-induced and photochemical reactions of heterohalomethanes with olefins was suggested by previous studies of the additions of carbon tetrachloride, carbon tetrabromide, chloroform, bromoform, and bromotrichloromethane to olefins (1). The addition reactions of bromodichloromethane with olefins, and the stepwise reaction of one molecule of dibromodichloromethane with two molecules of olefin are described in this paper. The possibility that the organic halides so formed might be hydrolyzable to 2-alkenals and α, α' -dienones stimulated interest in these addition reactions.

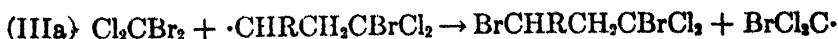
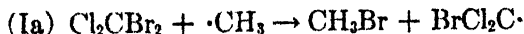
Reactions of bromodichloromethane with olefins. Acetyl peroxide-induced reactions of bromodichloromethane with propylene, isobutylene, and octene yielded the expected one-to-one molecular addition products, which were identified (as described in the experimental part) as 1,1-dichloro-3-bromoalkanes. The similar reaction with vinyl acetate yielded 1-bromo-3,3-dichloropropyl acetate.

With regard to ease of initiation, product yields, the nature of products formed, the reactions of bromodichloromethane resemble those of bromoform rather than those of chloroform. On the basis of product identification, and by analogy with the reaction mechanisms proposed for reactions previously studied, the following reaction chain is suggested for the bromodichloromethane addition reactions.



Together, the reactions of chloroform, bromoform, and bromodichloromethane establish the following order of reactivity toward free radicals: $\text{Br} > \text{H} > \text{Cl}$.

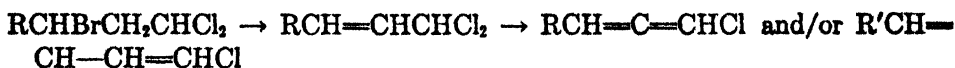
Reactions of dibromodichloromethane with olefins. Acetyl peroxide-induced reactions of dibromodichloromethane with propylene, isobutylene, and 1-octene also yielded one-to-one molecular addition products. With regard to ease of initiation and product yields, these reactions resemble those of carbon tetrabromide and bromotrichloromethane rather than those of carbon tetrachloride. On this basis the following reaction scheme is proposed, and product structures are assigned accordingly.



The addition products of dibromodichloromethane with propylene and isobutylene were induced to undergo similar addition reactions with the respective olefins. It is believed that the principal products obtained have the structures suggested by the following reaction scheme.



The difficulty in definitely identifying these products by the usual methods arises from the multiplicity of products obtained in the sodium ethoxide reactions. Even in the cases of the bromodichloromethane addition products, which yield chiefly the 2-alkenals, there are also low-boiling halogenated by-products, indicating side-reactions of the type:



With the addition products (one molecule of dibromodichloromethane to two molecules of the olefin) such side reactions predominate over the desired reactions which would lead to diethyl ketals of disubstituted divinyl ketones.

EXPERIMENTAL PART¹

The preparation of bromodichloromethane. Bromodichloromethane was prepared in the counterdistillation apparatus shown in Figure 1.² In a typical experiment, a solution containing bromoform (532 gr.; 2.1 moles), chloroform (800 gr.; 6.7 moles) and aluminum chloride (10 g.) was placed in flask *A*. It was heated to reflux for 30 minutes, and then stopcock *B* was opened to allow the distillate from the reaction mixture to flow through trap *C* which contained Florosil to remove traces of aluminum chloride. Finally, this distillate drained into flask *D*.

Distillation was continued until the temperature in the still-head above flask *A* reached 72–74°. At this time, flask *D* was heated to start distillation through fractionating column *E* (packed with single-turn glass helices). Pure chloroform was taken off at the top of the column, and returned through stopcock *F* and a connecting tube *G* to flask *A*. Stopcock *F* was adjusted so that the return of chloroform maintained a temperature of 72–74° above flask *A*.

After operating in this way for 40 hours, the volume of the reaction mixture (flask *A*) decreased to about 100 ml. Chloroform from the fractionating column was then drained

¹ The term Ag equiv. is defined as the number of grams of the halogen-containing compound which react with one mole of silver nitrate, in accordance with the reaction:



² This apparatus has been applied to the preparation of bromotrichloromethane in 90% yield by a similar method. It is also applicable to ester-exchange reactions (as in the conversion of ethyl to methyl esters), and to the Meerwein oxidation of high-boiling alcohols with the aid of acetone and aluminum *t*-butoxide.

rapidly into flask A until a volume of 500 ml. was reached. Counter-distillation was continued for another 8 hours. During this time, the distilling temperature above flask A dropped to 63°.

The solution in flask D was then distilled without further treatment. After unreacted chloroform had distilled, bromodichloromethane (b.p. 88°; n_D^{20} 1.4962; 903 g.; 87% yield) was obtained. The remaining solution was then distilled at reduced pressure. Dibromochloromethane (b.p. 62° at 120 mm.; n_D^{20} 1.5469; 70 g.; 11% yield) distilled next. A residue (15 g.) remained in the distilling flask.

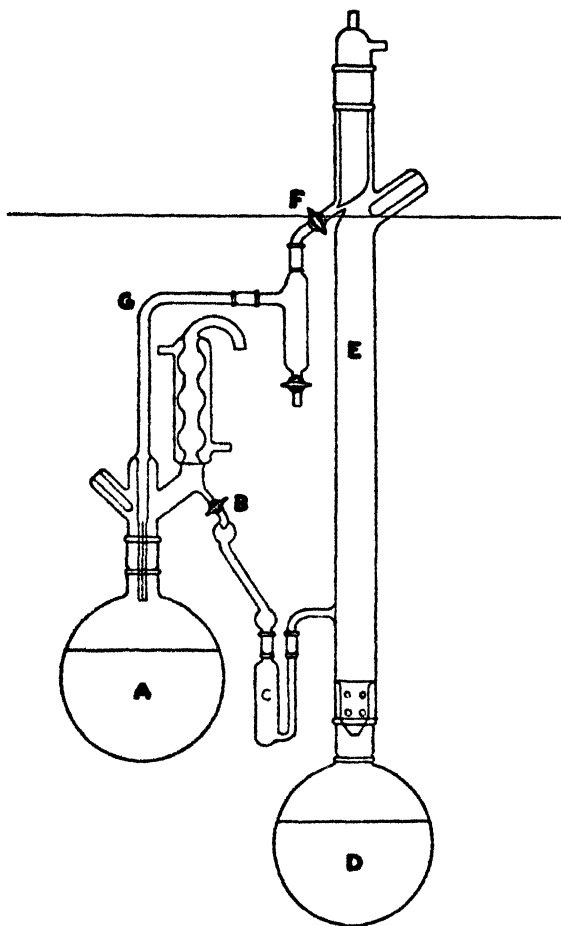


FIGURE 1

Reaction of bromodichloromethane with 1-octene in the presence of acetyl peroxide. A solution of bromodichloromethane (417.0 g.; 2.54 moles; n_D^{20} 1.4962) and 1-octene (56 g.; 0.5 mole; n_D^{20} 1.4000) held at 90° for 4 hours was treated with acetyl peroxide (5.4 g.; 0.046 mole) in two equal portions. After unchanged bromodichloromethane had been distilled, a product shown to be 1,1-dichloro-3-bromononane (110.1 g.; b.p. 65° at 0.03 mm.; n_D^{20} 1.4842) was recovered.

Anal. Calc'd for $C_9H_{17}BrCl_2$: Ag equiv., 92.0. Found: Ag equiv., 92.3.

A residue (17.5 g.) remained in the still pot.

Identification of the bromodichloromethane-1-octene addition product (1,1-dichloro-3-

bromononane). The bromodichloromethane-1-octene addition product (96.0 g.; 0.35 mole) was dropped into a sodium ethoxide solution (prepared by the reaction of 46 g. of sodium with 400 ml. of absolute ethanol) containing potassium iodide (5 g.). An exothermic reaction occurred, and a white solid separated. The reaction mixture was held at its reflux temperature for 10 hours.

After it had cooled, the white precipitate (81 g.; expected sodium salts, 93 g.) was separated on a filter. Ethanol was then removed by distillation through a 12-plate column until the volume of undistilled material was about 125 ml. Ligroin (b. 35°; 300 ml.) was added, and the resulting solution was washed with water. It was vigorously stirred with hydrochloric acid (3%) for 2 hours, and was then separated, washed with water, and dried over sodium sulfate.

After the ligroin had been removed by distillation, the reaction product was distilled through a 35-plate Podbielniak column. Fractions distilling first (b.p. 30–45° at 0.4 mm.; 12 g.) were unsaturated products containing halogen. The principal reaction product (b.p. 54–56° at 0.2 mm.; 34.1 g.; n_D^{20} 1.4501) then distilled. These physical constants correspond to those given in the literature for 2-nonenal.

Further confirmation for this identification was obtained by the preparation of the 2,4-dinitrophenylhydrazone (m.p. 124–25°; melting point of mixture with authentic 2,4-dinitrophenylhydrazone of 2-nonenal, 124–25°) and its *p*-nitrophenylhydrazone (m.p. 107–108°; melting point of mixture with authentic *p*-nitrophenylhydrazone of 2-nonenal, 107°). 2-Nonenal for this comparison was prepared according to the method of Scanlan and Swern (2).

Reaction of bromodichloromethane with vinyl acetate in the presence of acetyl peroxide. To a solution of vinyl acetate (50 g.; 0.58 mole; b.p. 72°; n_D^{20} 1.3951) in bromodichloromethane (375 g.; 2.29 moles) held at 65°, a solution of acetyl peroxide (2.5 g.) in bromodichloromethane (30 g.) was added slowly over a period of 4 hours. Following completion of the addition, the reaction mixture was heated for another 2 hours.

A mixture of unchanged vinyl acetate and bromodichloromethane (b.p. 40–48° at 100 mm.; 350 g.) was recovered by distillation through a 10-inch Vigreux column. Further distillation at lower pressures yielded a colorless liquid product (60 g.; b.p. 58–9° at 0.2 mm.; n_D^{20} 1.4785). This product gave a halogen analysis consistent with that expected for the bromodichloromethane-vinyl acetate addition product, 1-bromo-3,3-dichloropropyl acetate.

Anal. Calc'd for $C_5H_7BrCl_2O_2$: Ag equiv., 83.3. Found: Ag equiv., 82.9.

A residue (16.5 g.) remained in the distilling flask.

Identification of the bromodichloromethane-vinyl acetate addition product (1-bromo 3,3-dichloropropyl acetate). A portion (1 g.) of the bromodichloromethane-vinyl acetate addition product was treated with a solution of 2,4-dinitrophenylhydrazine (1.5 g.) and concentrated hydrochloric acid (2 ml.) in ethanol (95%, 30 ml.). The orange needles that separated melted at 162° after three recrystallizations from ethanol. This substance gave the halogen analysis expected for the 2,4-dinitrophenylhydrazone of β,β -dichloropropionaldehyde.

Anal. Calc'd for $C_5H_7Cl_2N_4O_4$: Cl, 23.1. Found: Cl, 22.9.

Attempts to prepare β,β dichloropropionaldehyde by the hydrolysis of this addition product failed, presumably because of its instability. Hydrolysis at room temperature with dilute sulfuric acid (5%) yielded only polymeric products. A similar result was obtained upon hydrolysis with dilute sodium bicarbonate solution. Accordingly, an attempt was made to hydrolyze, and then oxidize the resulting aldehyde to more stable products using a suspension of silver oxide in water.

A mixture containing the bromodichloromethane-vinyl acetate addition product (23 g.), silver oxide (62 g.) and water (150 g.) was shaken in a brown bottle for 6 hours at room temperature.

The mixture was filtered, and the filtrate was extracted several times with ether. The ether solution was dried over sodium sulfate and distilled, distillation yielding a high-boiling, tarry product (7.6 g.).

The filtrate and the precipitate were recombined, and the resulting mixture was saturated with potassium carbonate. After standing overnight, the precipitate was removed, and the filtrate was acidified with hydrochloric acid. It was then extracted several times with ether, and the ether solution was dried over sodium sulfate.

The ether left a dark, viscous residue (4 g.). White needle-like crystals (0.2 g.) sublimed from this residue when it was warmed under high vacuum. This substance melted at 78–79°. The melting point given in the literature for β -chloroacrylic acid is 80°.

Reaction of isobutylene with bromodichloromethane in the presence of acetyl peroxide. A solution of acetyl peroxide (2.3 g.) in bromodichloromethane (100 g.) was placed in the stainless steel bomb of a Parr hydrogenation apparatus. The apparatus was thoroughly swept with isobutylene, and the bomb and its contents were brought under a gauge pressure of 35 pounds of isobutylene. By means of an electrical heating jacket, the temperature of the reaction mixture was brought to 60°. The pressure of isobutylene was maintained at 35 pounds, and this temperature was held for 8 hours.

Unchanged bromodichloromethane (55 g.; b.p. 88°) was removed by distillation. The residual reaction product was distilled at reduced pressure. A colorless oil (b.p. 71–73° at 12 mm.; 34.6 g.; n_D^{20} 1.4950), which gave the halogen analysis expected for the bromodichloromethane-isobutylene addition product, was obtained.

Anal. Calc'd for $C_4H_7BrCl_2$: Ag equiv., 73.3. Found: Ag equiv., 72.0.

A tarry residue (5 g.) remained in the distilling flask.

Identification of the bromodichloromethane-isobutylene addition product (1,1-dichloro-3-methyl-3-bromobutane). A portion (14 g.) of the bromodichloromethane-isobutylene addition product was dropped slowly into a sodium ethoxide solution prepared by dissolving sodium (9 g.) in absolute ethanol (200 ml.). The reaction mixture warmed, and a white precipitate appeared. The reaction mixture was heated under reflux for 12 hours. After it cooled, the precipitated salts (9.5 g.; 12.1 g. expected) were separated and the filtrate was distilled under reduced pressure (100 mm.) to remove ethyl alcohol. When the volume of the mixture in the distilling flask reached 50 ml., ligroin (b. 35°; 150 ml.) was added. The ligroin solution was washed with water, dilute hydrochloric acid, and again with water, and was dried over sodium sulfate.

After the ligroin had been removed by distillation, an oily product remained. It distilled from 50° to 70° at 50 mm. (6 g.; n_D^{20} 1.4446). This oil was shown to contain β,β -dimethylacrolein by conversion to its dark red 2,4-dinitrophenylhydrazone (m.p. 178.5–179°; melting point of mixture with authentic 2,4-dinitrophenylhydrazone of β,β -dimethylacrolein, 178.5–179°).

β,β -dimethylacrolein used for comparison was prepared by the method of Fischer, Ertel, and Loewenberg (3).

Reaction of bromodichloromethane with propylene in the presence of acetyl peroxide. A solution of acetyl peroxide (2.2 g.) in bromodichloromethane (167.4 g.; 1.02 mole) was treated with propylene in a Parr bomb apparatus in a manner similar to that described for the isobutylene reaction. A pressure of 45 pounds and a reaction temperature of 60° were maintained for 10 hours.

The reaction mixture was distilled through a 10-inch Vigreux column. After unchanged bromodichloromethane (b.p. 25–28° at 30 mm.; 114. g.) had been removed, a colorless oil (34.3 g.; b.p. 75–76° at 30 mm.; n_D^{20} 1.4912), which gave a halogen analysis consistent with 1,1-dichloro-3-bromobutane, distilled.

Anal. Calc'd for $C_4H_7BrCl_2$: Ag equiv., 68.6. Found: Ag equiv., 68.5.

A residue (11.3 g.) remained in the distilling flask.

Identification of the bromodichloromethane-propylene addition product (1,1-dichloro-3-bromobutane). A portion (30 g.) of the bromodichloromethane-propylene addition product was dropped into a solution of the sodium salts of ethylene glycol prepared by the reaction of 19 g. of sodium with 250 g. of ethylene glycol held at 90–100°, and the resulting reaction mixture was held at 110° for 5 hours. After cooling, the mixture was acidified with dilute hydrochloric acid (5%), and the resulting solution was distilled under vacuum (110 mm.). An aqueous solution (73 ml.), smelling strongly of an aldehyde, was obtained. An aliquot

portion (5 ml.) of this solution was treated with an excess of 2,4-dinitrophenylhydrazine. A crimson precipitate (0.4523 g.; yield, 28%) was obtained. This material was shown to be the 2,4-dinitrophenylhydrazone of crotonaldehyde (m.p. 189° after three recrystallizations from a benzene-ligroin solution; melting point of mixture with an authentic sample, 189°).

Reaction of dibromodichloromethane with propylene in the presence of acetyl peroxide. A solution of acetyl peroxide (2 g.) in dibromodichloromethane (203.4 g.; b.p. 68° at 88 mm.; n_D^{20} 1.5509) was placed in the bomb of the Parr hydrogenation apparatus. After the apparatus was thoroughly swept with propylene, a pressure of 30 pounds of propylene was maintained, and the reaction mixture was held at 80° for 4 hours.

The reaction mixture (wt. after reaction, 232 g.) was distilled at reduced pressure. Unchanged dibromodichloromethane (16 g.; b.p. 68° at 88 mm.) distilled first. The reaction product (b.p. 36° at 0.05 mm.; 214.7 g.; n_D^{20} 1.5369) was a colorless oil which gave the correct halogen analysis and molecular weight for the dibromodichloromethane-propylene addition product (1,1-dichloro-1,3-dibromobutane).

Anal. Calc'd for $C_4H_8Br_2Cl_2$: Ag equiv., 69.7; mol. wt., 279.

Found: Ag equiv., 69.2; mol. wt., 275.

A residue (10 g.) remained.

This substance was also prepared by photochemically-induced addition. Dibromodichloromethane (300 g.) was placed in a tube illuminated internally with a mercury-vapor discharge tube. Propylene was slowly passed into the solution while heat from the light maintained the reaction mixture at 50°. These conditions were maintained for 60 hours. 1,1-Dichloro-1,3-dibromobutane (145.5 g.) was obtained by distillation.

Reaction of 1,1-dichloro-1,3-dibromobutane with propylene in the presence of acetyl peroxide. In 1,1-dichloro-1,3-dibromobutane (120.0 g.) prepared in the previous reaction, acetyl peroxide (2 g.) was dissolved, and the solution was placed in the steel bomb of the Parr apparatus. The reaction mixture was held at 80° for 10 hours under a 40-pound pressure of propylene.

The reaction mixture was distilled without further treatment under high vacuum. Unchanged 1,1-dichloro-1,3-dibromobutane (53.5 g.; b.p. 36–49° at 0.5 mm.) was removed. A colorless oil (b.p. 75–78° at 0.5 mm.; 58.5 g.; n_D^{20} 1.5282) then distilled. It gave the halogen analysis and molecular weight expected for 2,6-dibromo-4,4-dichloroheptane.

Anal. Calc'd for $C_7H_{12}Br_2Cl_2$: Ag equiv., 81.7; mol. wt., 326.

Found: Ag equiv., 81.3; mol. wt., 321.

A residue (7 g.) remained in the distilling flask.

Reaction of 1,1-dichloro-1,3-dibromobutane with 1-octene in the presence of acetyl peroxide. A solution of acetyl peroxide (2 g.) in 1,1-dichloro-1,3-dibromobutane (285 g.; 0.69 mole) and 1-octene (20.0 g.; 0.18 mole) was held at 70° for 10 hours, and then at 100° for 3 hours.

The reaction mixture was then distilled. About 6.0 g. of 1-octene (b.p. 32–40° at 43 mm.) was recovered. Unchanged 1,1-dichloro-1,3-dibromobutane (206. g.; 0.52 mole; b.p. 62–67° at 1 mm.) distilled next. The residual reaction product (44.1 g.; 62% yield) had too high a boiling point to permit of distillation at 0.1 mm. through the Vigreux column. Accordingly, it was distilled in a molecular still at a pressure of 10^{-6} mm. Hg. A colorless oil (41.2 g.; n_D^{20} 1.5120), which gave a halogen analysis and a molecular weight consistent with 2,6-dibromo-4,4-dichlorododecane, was obtained.

Anal. Calc'd for $C_{12}H_{22}Br_2Cl_2$: Ag equiv., 99.3; mol. wt., 397.

Found: Ag equiv., 99.5; mol. wt., 396.

Reaction of dibromodichloromethane with isobutylene in the presence of acetyl peroxide. A solution of acetyl peroxide (2.8 g.) in dibromodichloromethane (143. g.) was placed in the steel bomb of the Parr apparatus. A small amount of isobutylene introduced into the bomb dissolved completely. The bomb and its contents were slowly warmed to 50°, and pressure in the bomb increased from 0 to 18 pounds. At this point, the pressure rose suddenly to 45 pounds and then dropped to 0. At the same time, the reaction mixture increased in temperature to 90°. The bomb heater was turned off, and the temperature of the reaction mixture was maintained at 70° by the slow introduction of isobutylene. Finally, it was

necessary to turn on the bomb heater to hold the reaction temperature at 70°, and a pressure of 20 pounds of isobutylene was maintained for two hours.

The reaction mixture was distilled through a 10-inch Vigreux column. Unchanged dibromodichloromethane (15 g.; b.p. 65° at 80 mm.) was recovered. Then a colorless oil (143 g., b.p. 53° at 0.3 mm.; n_D^{20} 1.5385), which gave a halogen analysis consistent with 1,1-dichloro-1,3-dibromo-3-methylbutane, distilled.

Anal. Calc'd for $C_4H_8Br_2Cl_2$: Ag equiv., 74.7. Found: Ag equiv., 74.5.

A residue (9 g.) remained in the distilling flask.

Reaction of 1,1-dichloro-1,3-dibromo-3-methylbutane with isobutylene in the presence of acetyl peroxide. A solution of acetyl peroxide (3.6 g.) in 1,1-dichloro-1,3-dibromo-3-methylbutane (110 g.) was placed in the steel bomb of the Parr apparatus. The temperature of the reaction mixture was held at 65°, and the isobutylene pressure was maintained at 23 pounds for 12 hours.

The reaction mixture was distilled through a 10-inch Vigreux column. Unchanged 1,1-dichloro-1,3-dibromo-3-methylbutane (b.p. 50–53° at 0.3 mm.; 95 g.) distilled first. Since on further distillation, decomposition of the residue (30 g.) occurred, it was distilled in a Hickman molecular still. A colorless oil (22 g.; n_D^{20} 1.5342), which gave a halogen analysis corresponding to 2,6-dibromo-2,6-dimethyl-4,4-dichloroheptane, was obtained.

Anal. Calc'd for $C_8H_{14}Br_2Cl_2$: Ag equiv., 88.7. Found: Ag equiv., 88.5.

A residue (7 g.) remained in the still.

Attempts to identify the 1,1-dichloro-1,3-dibromo-3-methylbutane-isobutylene addition product. A solution containing this addition product (38. g.; 0.107 mole) in 95% ethanol (100 ml.) was placed in a 500-ml. round-bottomed flask fitted with a Tru-Bore stirrer. The flask was immersed in an ice-water bath, and the solution was vigorously stirred. Ethanolic potassium hydroxide solution (236 ml.; 0.904 N; 0.2133 mole KOH) was slowly dropped in over a period of 1 hour. A white precipitate formed. After the addition was completed the reaction mixture was allowed to stand at room temperature for 16 hours.

Water (300 ml.) was then added to the reaction mixture, and the resulting mixture was extracted 5 times with 200-ml. portions of ligroin (b. 60°). The ligroin solution was then washed three times with water, and was dried over sodium sulfate.

An aliquot portion of the combined wash liquors was analyzed for halogen content. It was found that 0.2133 equivalent of halide ion had been removed in the hydrolysis (theoretical amount based upon potassium hydroxide used, 0.2133 equivalent). Further analysis indicated that this solution contained 0.06012 equivalent of chloride ion, and 0.1533 equivalent of bromide ion.

Ligroin was removed by distillation through a 25-plate Podbielniak column. The remaining reaction product was then distilled through a 10-inch Vigreux column. Four fractions which boiled over a range from 55° to 110° at 24 mm. were obtained (combined wt., 14.5 g.). Fraction 3 (5.5 g.; n_D^{20} 1.4821; b.p. 87–96° at 24 mm.) was analyzed for chlorine.

Anal. Calc'd for $C_8H_{14}Cl_2$: Cl, 36.8. Found: Cl, 34.3.

The apparent chlorine content obtained by analysis of a substance $C_8H_{14}BrCl$ would be 34.4.

SUMMARY

1. In peroxide-induced reactions with 1-alkenes, bromodichloromethane closely resembles bromoform (rather than chloroform) in its behavior.
2. Based upon experimental evidences of structure, it is concluded that bromodichloromethane adds in good yield (50–80%) to 1-alkenes to give the following products: with 1-octene, 1,1-dichloro-3-bromononane; with propylene, 1,1-dichloro-3-bromobutane; with isobutylene, 1,1-dichloro-3-bromo-3-methylbutane; and with vinyl acetate, 1-bromo-3,3-dichloropropyl acetate.
3. Dibromodichloromethane reacts with propylene in the presence of acetyl

peroxide, or under illumination, to give 1,1-dichloro-1,3-dibromobutane. This product reacts with propylene under the same conditions to give 2,6-dibromo-4,4-dichloroheptane. It reacts with 1-octene to give 2,6-dibromo-4,4-dichlorododecane.

4. Free-radical chain mechanisms for these reactions are discussed.

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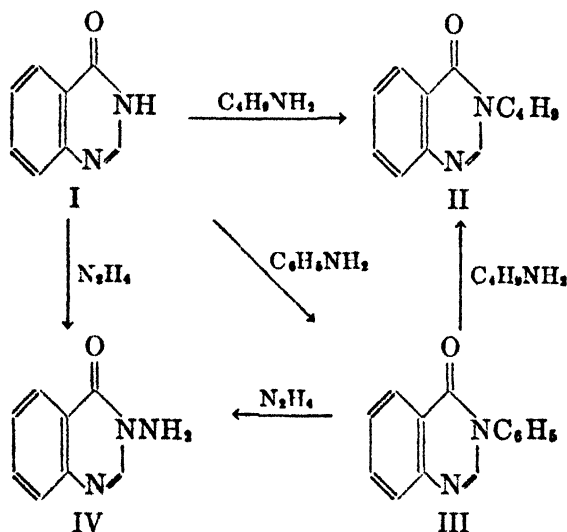
REACTIONS OF 4-QUINAZOLONE. IV. REPLACEMENTS AT THE 3-POSITION

NELSON J. LEONARD AND WILLIAM V. RUYLE

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Since 4-quinazolone (I) has been found to react with primary and secondary alkylamines (1, 2), it was of interest to examine the reaction of 4-quinazolone with primary arylamines and other NH_2 -functions and to determine the order of replacement of different groups at the 3-position.

The following facts were previously known. The 3-NH of 4-quinazolone could be replaced by NC_6H_5 , through treatment of I with butylamine, to give II (1). The replacement of a 3-NH group by NNH_2 was discovered by Kunckell



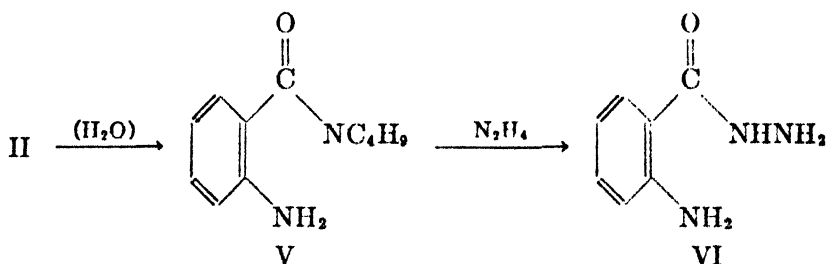
(3). He found that benzoyleneurea and hydrazine hydrate gave 3-amino-2,4-quinazolinedione (4) and that 1-methylbenzoyleneurea and hydrazine hydrate gave 3-amino-1-methyl-2,4-quinazolinedione (5). The replacement of the 3- NC_6H_5 in 3-phenyl-2,4-quinazolinedione by NNH_2 was also realized by Kunckell (5). The same replacement in 3-phenyl-4-quinazolone (III) was effected by Cairncross and Bogert (6), who identified their product, and thus the earlier product of Paal and Busch (7), as 3-amino-4-quinazolone (IV).

The replacement of 3- NC_6H_5 by NNH_2 (conversion of III to IV) has been repeated in order to show that a short period at the reflux temperature is just as effective (eighty-nine per cent yield) as lengthy heating in a sealed tube. The replacement of 3-NH by NC_6H_5 (conversion of I to III) has been shown to proceed to forty per cent yield. 3-Phenyl-4-quinazolone (III)¹ had been prepared

¹ Compound III was found to be about equal to aspirin in lowering the temperatures of febrile rats. We are grateful to Dr. K. K. Chen of the Lilly Research Laboratories for pharmacological testing.

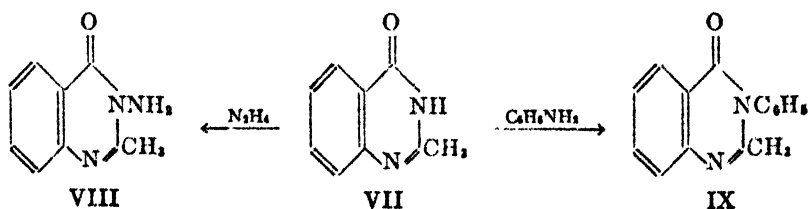
previously by unequivocal methods (6, 8). The replacement of 3-NH by NNH_2 (conversion of I to IV) was effected readily when I was heated under reflux for thirty minutes with hydrazine hydrate, to give a seventy-five per cent yield of 3-amino-4-quinazoline (IV). The product had been synthesized previously by Thode (9). Finally, the replacement of 3- NC_6H_5 by NC_4H_9 (conversion of III to II) was effected when III was heated in a sealed tube with butylamine, to give a thirty-six per cent yield of 3-butyl-4-quinazoline (II). These interconversions were the only ones which could be realized within the group of 4-quinazolones I, II, III, and IV. Only the reactions indicated in the diagram could be forced to take place to any determinable degree. Since reversal of these replacements at the 3-position did not proceed (see Table I), the reaction between 4-quinazolones and amines appears not to be a simple equilibrium system.

It has been established in these experiments that the order of replacement at the 3-position of 4-quinazoline is: NH , NC_6H_5 , $\left\{ \begin{smallmatrix} \text{NNH}_2 \\ \text{NC}_4\text{H}_9 \end{smallmatrix} \right\}$, wherein each group can replace the one (or two) preceding. The position of NNH_2 and NC_4H_9 with respect to each other is undecided. Hydrazine displaces ammonia and aniline from the quinazolones much more readily than does butylamine. Moreover, although butylamine gave no reaction with 3-amino-4-quinazoline, hydrazine hydrate in lengthy refluxing with 3-butyl-4-quinazoline (II) gave anthranilhydrazide (VI) and a small amount of N-(2-aminobenzoyl)butylamine (V).



In accounting for the formation of the hydrazide VI, the presence of a small amount of the amide V suggests that the displacement of butylamine occurred at this stage rather than in an initial reaction of hydrazine with 3-butyl-4-quinazolinone.

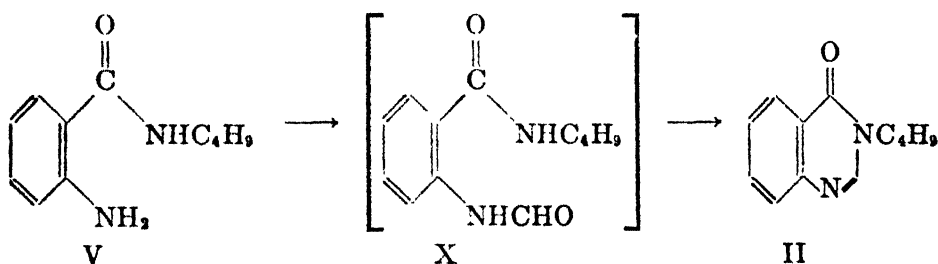
In a series of reactions of amine functions with 2-methyl-4-quinazolinone (VII), hydrazine was again found to be the most efficient in replacing the 3-NH group. The product was 3-amino-2-methyl-4-quinazolinone (VIII).



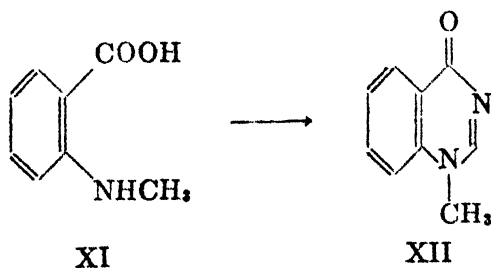
Aniline caused replacement of the 3-NH by NC_6H_5 to give 2-methyl-3-phenyl-4-quinazolone (IX), but butylamine caused no replacement of the 3-NH by NC_4H_9 under the conditions employed. The reaction of VII with piperidine, which would be expected to yield a more stable ring-opened intermediate than the reaction of I with piperidine (2), could not be forced to take place.

The unique effectiveness of hydrazine, in displacing ammonia from 4-quinazolone and 2-methyl-4-quinazolone and aniline from 3-phenyl-4-quinazolone, 3-phenyl-2,4-quinazolinedione, benzoyleneurea, and 1-methylbenzoyleneurea, probably lies in the preferential splitting out of ammonia or the amine after the hydrazine has added to the 4-carbonyl group. Analogous preferential splitting out of water occurs after the addition of hydrazine to carbonyl groups in the facile formation of hydrazones and azines.

It was found possible to make 3-butyl-4-quinazolone (II), which had been synthesized previously (1, 10) and which was used in the replacement studies, by a Niementowski reaction (11) from *N*-(2-aminobenzoyl)butylamine (V) and formamide. The conversion of V to II probably proceeds through *N*-(2-formylaminobenzoyl)butylamine (X), formed by the action of formamide as aquoammonoformic acid. Such a course for this reaction is consistent with the mechanism of the Niementowski ring-closure as established by Meyer and Wagner (12).



The Niementowski reaction was also shown to be applicable to the formation of a 1-alkyl-4-quinazolone from the corresponding *N*-alkylantranilic acid. When *N*-methylantranilic acid (XI) was heated with formamide under conditions which suffice for quinazolone formation in the usual Niementowski ring-closure (125° , four hours), most of the *N*-methylantranilic acid was recovered unchanged. The reaction product, isolated in very small yield, was shown to be the *N*-methylantranilic acid salt of 1-methyl-4-quinazolone.



By increasing the time of heating the reactants to eighteen hours, 1-methyl-4-quinazolone (XII), m.p. $136\text{--}137^\circ$, could be obtained in thirty per cent yield.

This compound had been prepared by Knapé (13), from other reactants, in an amount insufficient for analysis and of a doubtful degree of purity, since he reported a lower melting point (123–124°).² Our product (XII) was further characterized by the formation of the hydrochloride and picrate.

EXPERIMENTAL³

The results of heating 4-quinazolones with various amine functions are assembled in Table I. Wherever the absence of a product is indicated, the only isolable substance was the starting material. Although the conditions of each reaction are included in Table I, it is also necessary to describe representative procedures in some detail because of the differing isolation problems encountered.

Reactions of 4-quinazolones with n-butylamine. The reaction of 4-quinazolone with n-butylamine has been reported previously (1).

A mixture of 4.0 g. (0.018 mole) of 3-phenyl-4-quinazolone and 11.1 g. (0.15 mole) of n-butylamine was heated in a sealed tube at 150° for twenty-four hours. There was no excess pressure in the tube when it was opened. The reaction mixture, which was a pale yellow liquid, was distilled at ordinary pressure until most of the n-butylamine had been removed. A second fraction distilled at 75–77° (15 mm.), 60–61° (6 mm.). This fraction weighed 0.60 g. (36%), and was identified as aniline by conversion to acetanilide. The residue from the distillation, which was a viscous oil, was extracted repeatedly with 10-ml. portions of boiling petroleum ether, (b.p. 40–60°). After several such extractions, the insoluble material solidified. Three recrystallizations of this solid from benzene-petroleum ether yielded 0.38 g. (10%) of anthranilanilide, m.p. 130–131°.

Anal. Calc'd for $C_{11}H_{12}N_2O$: C, 73.56; H, 5.70.

Found: C, 73.57; H, 5.84.

From the petroleum ether extracts, 1.33 g. (36%) of 3-butyl-4-quinazolone, m.p. 71–72°, was obtained by fractional crystallization from petroleum ether. Approximately 1.5 g. of viscous oil was also obtained which could not be made to crystallize.

When 3-amino-4-quinazolone and 2-methyl-4-quinazolone were heated with n-butylamine under similar conditions, 96% and 92%, respectively, of the quinazolones were recovered unchanged. No other products were isolated.

Reactions of 4-quinazolones with aniline. A mixture of 5.0 g. (0.034 mole) of 4-quinazolone and 9.5 g. (0.1 mole) of aniline was heated under reflux for twenty-four hours in an oil-bath maintained at 200–210°. Evolution of ammonia was observed. The crude mixture was worked up as with the earlier 4-quinazolone-amine reactions through the benzene extraction procedure (2). The combined benzene extracts were boiled five minutes with activated charcoal. The charcoal was removed and the benzene was distilled under reduced pressure. The residue was recrystallized from ether, then from ethanol, as colorless platelets, m.p. 136.5–137.5°. Clark and Wagner (8) reported the melting point 136–136.5° for 3-phenyl-4-quinazolone.

The reaction of 3-butyl-4-quinazolone with aniline was carried out in a similar manner. After removal of the aniline by distillation, a dark brown semi-solid mixture remained which was treated with activated charcoal and recrystallized from benzene-petroleum ether to give 67% recovery of 3-butyl-4-quinazolone as the only isolable compound.

¹ Knapé (13) reported the melting point 70–71° for 3-methyl-4-quinazolone. Bogert and Geiger (14) later showed that this material was actually the hydrate of 3-methyl-4-quinazolone, and that the anhydrous substance melted at 105°. Our tardy recognition of the corrective work of Bogert and Geiger allows us now to assign the 3-methyl-4-quinazolone structure to the "unknown" isomer, m.p. 103.5–105.5° obtained by Leonard and Curtin (1) along with 4-methoxyquinazolone in the treatment of 4-quinazolone with diazomethane.

² All melting points are corrected. Microanalyses by Miss Theta Spoor.

Similarly, from the reaction of 3-amino-4-quinazolone with aniline, 57% of the starting material was isolated, but no other product.

When the reaction of 2-methyl-4-quinazolone with aniline was carried out under similar conditions, 2-methyl-3-phenyl-4-quinazolone was obtained and was identified by melting point and mixed melting point (145–146°) with the compound prepared by an unequivocal method (17).

Reactions of 4-quinazolones with hydrazine hydrate. A mixture of 20 g. (0.136 mole) of 4-quinazolone and 55 g. of hydrazine hydrate (85% in water) was heated under reflux. The

TABLE I
REACTIONS OF AMINES WITH 4-QUINAZOLONES

AMINE	SUBSTITUTED 4-QUINAZOLONE	CONDITIONS*	PRODUCT	YIELD, %†	RECOVERY OF QUINAZOLONE, %
C ₄ H ₉ NH ₂	4-Quinazolone	S, 150°, 24 hrs.	3-Butyl-4-quinazolone	36	?
C ₆ H ₅ NH ₂	3-Phenyl-	S, 150°, 24 hrs.	3-Butyl-4-quinazolone	36 (36)	—
			Anthranilanilide	10	—
C ₆ H ₅ NH ₂	3-Amino-	S, 150°, 24 hrs.	—	—	96
C ₆ H ₅ NH ₂	2-Methyl-	S, 150°, 24 hrs.	—	—	92
C ₆ H ₅ NH ₂	4-Quinazolone	R, 200°, 24 hrs.	3-Phenyl-4-quinazolone	26 (40)	34
C ₆ H ₅ NH ₂	3-Butyl-	R, 200°, 24 hrs.	—	—	67
C ₆ H ₅ NH ₂	3-Amino-	R, 200°, 24 hrs.	—	—	57
C ₆ H ₅ NH ₂	2-Methyl-	R, 200°, 24 hrs.	2-Methyl-3-phenyl-4-quinazolone	17 (40)	58
N ₂ H ₄ ·H ₂ O	4-Quinazolone	R, 120°, 0.5 hr.	3-Amino-4-quinazolone	75 (75)	—
N ₂ H ₄ ·H ₂ O	3-Butyl-	R, 120°, 2 hrs.	—	—	95
		R, 120°, 24 hrs.	Anthranilhydrazide	37	—
			N-(2-Aminobenzoyl)butylamine	5	—
N ₂ H ₄ ·H ₂ O	3-Phenyl-	R, 120°, 0.25 hr.	3-Amino-4-quinazolone	89 (89)	—
N ₂ H ₄ ·H ₂ O	2-Methyl-	R, 120°, 2.5 hrs.	3-Amino-2-methyl-4-quinazolone	29 (39)	24
C ₆ H ₁₀ NH	2-Methyl-	S, 175°, 24 hrs.	—	—	91
α-C ₆ H ₄ N-NH ₂	4-Quinazolone	S, 155°, 24 hrs.	—	—	68
α-C ₁₀ H ₇ NH ₂	4-Quinazolone	S, 200°, 16 hrs.	—	—	56

* S = Sealed tube, R = reflux.

† Figure in parentheses is the yield based upon unrecovered starting quinazolone.

4-quinazolone dissolved quickly and after ten minutes white needles began to separate from the mixture, which soon became almost solid. The mixture was filtered and the filtrate was heated under reflux for twenty minutes. More of the product separated on cooling. The combined weight of the two crops was 16.2 g. (75%), m.p. 205–208°. Recrystallization from 95% ethanol gave glistening colorless needles of 3-amino-4-quinazolone, m.p. 209–210° [reported by Cairncross and Bogert (6), 211°]. When this material was heated with benzaldehyde and the product was recrystallized from ethanol, shining colorless leaflets of 3-benzalamino-4-quinazolone, m.p. 127–128° were obtained [reported by Thode (9), 129°].

In the attempted reaction of 3-butyl-4-quinazolone with hydrazine hydrate under similar conditions (two hours under reflux) a 95% recovery of starting material was realized. However, when the reaction mixture was heated under reflux for twenty-four hours, *N*-(2-aminobenzoyl)butylamine, m.p. 85–86° (5% yield) and anthranilhydrazide, m.p. 121–122° (37% yield) were obtained.

A mixture of 1 g. of 3-phenyl-4-quinazolone and 3 g. of hydrazine hydrate was heated under reflux for fifteen minutes. The crystals which separated were removed by filtration, washed with water, recrystallized from ethanol, and identified as 3-amino-4-quinazolone, m.p. 209–210°. The presence of aniline in the aqueous ethanol filtrates was established by the formation of acetanilide.

When 1 g. of 2-methyl-4-quinazolone was heated under reflux with 3 g. of hydrazine hydrate (85% in water) the 2-methyl-4-quinazolone dissolved slowly. After the mixture had been heated for two and one-half hours, it was cooled. Colorless needles separated which, after recrystallization, first from benzene then from ethanol, melted at 147–148° [reported for 3-amino-2-methyl-4-quinazolone by Bogert and Gortner (15), 152°]; yield, 0.32 g. (39% based on unrecovered 2-methyl-4-quinazolone). The product was heated with benzaldehyde to obtain 3-benzalamino-2-methyl-4-quinazolone, m.p. 184–186° [reported by Bogert, Beal, and Amend (16), 187°].

N-(2-Nitrobenzoyl)butylamine. This compound, which apparently has not been previously prepared, was obtained by the same method as that used for *N*-(2-nitrobenzoyl)-piperidine (2). The yield from 50 g. (0.3 mole) of 2 nitrobenzoic acid was 48 g. (73%) of colorless prisms, m.p. 55–57°.

Anal. Calc'd for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.40; N, 12.61.

Found: C, 59.56; H, 6.10; N, 12.41.

Satisfactory identification was established in the reduction of the nitro compound to the known amino compound.

N-(2-Aminobenzoyl)butylamine. This compound has been prepared previously but by a different method (8). *N*-(2-Nitrobenzoyl)butylamine (44.2 g., 0.2 mole) was dissolved in 200 ml. of ethanol, 0.2 g. of platinum oxide catalyst was added, and the hydrogenation was carried out at 25° and 3–4 atmospheres. The hydrogen was absorbed rapidly and it was necessary to interrupt the shaking intermittently in order to prevent overheating. The catalyst and the solvent were removed and the residue was digested on a steam-bath for a few minutes with 100 ml. of low-boiling petroleum ether. The mixture was cooled and the voluminous mass of pink crystals was collected. The material retained on the filter was of a waxy nature and was very difficult to free from solvent. The yield of product, m.p. 84–86°, was 34.5 g. (90%). The pink color of the material was persistent and was not removed by recrystallization and attempted charcoal decolorization from either dilute ethanol or high-boiling petroleum ether. A colorless product was obtained by dissolving the material in dilute hydrochloric acid, treating with charcoal, filtering, and reprecipitating by the addition of aqueous sodium hydroxide. Recrystallization of the colorless material from high-boiling petroleum ether gave a pure product, m.p. 85–86°.

Reaction of N-(2-aminobenzoyl)butylamine with formamide. 3-Butyl-4-quinazolone. *N*-(2-Aminobenzoyl)butylamine (5 g., 0.026 mole) and formamide (3 g., 0.067 mole) were heated together for six hours in a large test-tube suspended in an oil-bath at 170°. Ammonia was evolved during this reaction period. Upon the addition of 20 ml. of water and 3–4 drops of ammonium hydroxide to the cooled mixture, a crystalline solid was obtained. The yield of crude product was 4.6 g. (88%). After two recrystallizations from 50% aqueous ethanol, the melting point was 72–73°. Bogert and May (10) reported the melting point 71–72° for 3-butyl-4-quinazolone. There was no depression of melting point when this product was mixed with an authentic sample of 3-butyl-4-quinazolone (1).

Reaction of N-methylantranilic acid with formamide. 1-Methyl-4-quinazolone. A mixture of 10 g. (0.066 mole) of *N*-methylantranilic acid and 6.25 g. (0.14 mole) of formamide was heated under an air condenser at 130° for eighteen hours. The reaction mixture was subjected to vacuum distillation (bath temp. 145°, 7 mm.) to remove excess formamide.

The residual oil partially crystallized on standing two days in the refrigerator. The mixture was triturated with 10 ml. of cold benzene and was filtered. The greyish gummy crystals were dissolved in a boiling mixture of 20 ml. of benzene and 5 ml. of ethanol. After cooling slightly, 15 ml. of petroleum ether (b.p. 40–60°) was added. The solvent layer was decanted from the oil which first separated, and was cooled slowly. The colorless needles which formed were recrystallized from benzene-ether; m.p. 132–135°. A final recrystallization from benzene gave 0.86 g. (8%) of colorless elongated prisms, m.p. 136–137°.

Anal. Calc'd for $C_8H_5N_3O$: C, 67.48; H, 5.03; N, 17.49.

Found: C, 67.31; H, 4.98; N, 17.62.

This compound was very deliquescent. It was soluble in water and ethanol and only slightly soluble in benzene, ether, and petroleum ether. It formed a *picrate* from ethanol solution as fine yellow needles, m.p. 246–247° (dec.).

Anal. Calc'd for $C_{11}H_7N_5O_6$: C, 46.28; H, 2.85.

Found: C, 46.28; H, 2.76.

The *hydrochloride* was prepared by treating the compound with concentrated hydrochloric acid, from which the salt separated as rectangular prisms. These were recrystallized from 95% ethanol; m.p. 245–246°.

Anal. Calc'd for $C_8H_5ClN_3O$: C, 54.97; H, 4.61.

Found: C, 54.82; H, 4.89.

Since it was impractical to isolate more of the pure 1-methyl-4-quinazolone from the mother liquors, these were converted—one portion to the hydrochloride (1.54 g., 12%), and the other to the picrate (2.68 g., 10%). The total yield of 1-methyl-4-quinazolone, its hydrochloride, and picrate was thus 30%.

In another experiment, 5 g. of *N*-methylantranilic acid and 3 g. of formamide were heated at 125° for four hours. When the reaction mixture was cooled, greyish crystals formed, which were recrystallized from ethanol and then from benzene, m.p. 135–136°; yield, 0.72 g.

Anal. Calc'd for $C_{17}H_{17}N_3O_2$: C, 65.58; H, 5.51; N, 13.50.

Found: C, 65.74; H, 5.71; N, 13.56.

The nature of the compound was indicated by the fact that a mixture of equimolar portions of *N*-methylantranilic acid and 1-methyl-4-quinazolone started to melt below 100° but resolidified and melted completely at 134–135°. When the melt was recrystallized from benzene, its appearance and melting point were identical with those of the reaction product, m.p. 135–136°, and the melting point was not depressed by admixture of the two samples,

SUMMARY

1. It has been established that the order of replacement at the 3-position of 4-quinazolone is: NH , NC_6H_5 , $\left\{ \begin{matrix} NNH_2 \\ NC_4H_9 \end{matrix} \right\}$, wherein each group can replace the one (or two) preceding.

2. It has been shown that hydrazine can readily replace the 3- NH or 3- NC_6H_5 group in 4-quinazolone, 3-phenyl-4-quinazolone, and 2-methyl-4-quinazolone by NNH_2 .

3. The Niementowski reaction has been extended to the synthesis of representative 1-alkyl- and 3-alkyl-4-quinazolones.

URBANA, ILLINOIS

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THE CYANOETHYLATION OF CERTAIN KETONES, β -DIKETONES, AND β -KETO ESTERS¹

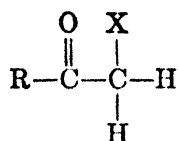
GLENN R. ZELLARS AND ROBERT LEVINE

Received July 23, 1948

Bruson and Riener (1, 2, 3, 4) have recently reported the cyanoethylation of ketones, cyanoesters, nitroparaffins, aldehydes, and two β -keto esters with acrylonitrile in the presence of the basic condensing agents, potassium hydroxide, sodium methoxide, and benzyltrimethylammonium hydroxide (Triton B).

In the present investigation the cyanoethylation of a number of β -keto esters, β -diketones, and methyl ketones has been studied in the presence of Triton B and benzyltrimethylammonium butoxide (BTAB) as the condensing agents.

The general structure of the active hydrogen compounds studied may be represented by the following formula:

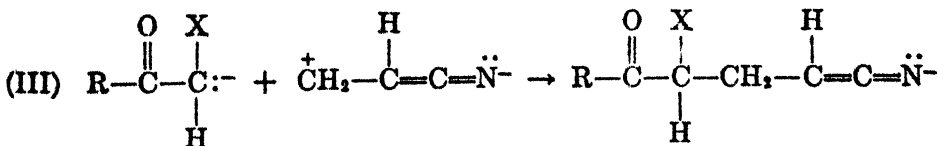
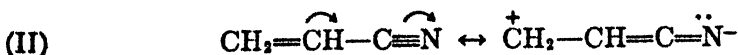
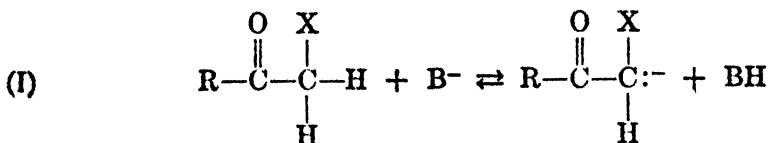


If $\text{X} = \begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{R} \end{array}$, the compound is a β -diketone.

If $\text{X} = \begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{OC}_2\text{H}_5 \end{array}$, the compound is a β -keto ester.

If $\text{X} = \text{H}$, the compound is a methyl ketone.

The mechanism for the cyanoethylation probably involves the following steps, where $\text{B} = \text{OH}^-$ or $\text{OC}_2\text{H}_5\text{-n}^-$



¹ This work is based on a thesis submitted by Glenn R. Zellars in partial fulfillment of the requirements for the degree of Master of Science at the University of Pittsburgh.

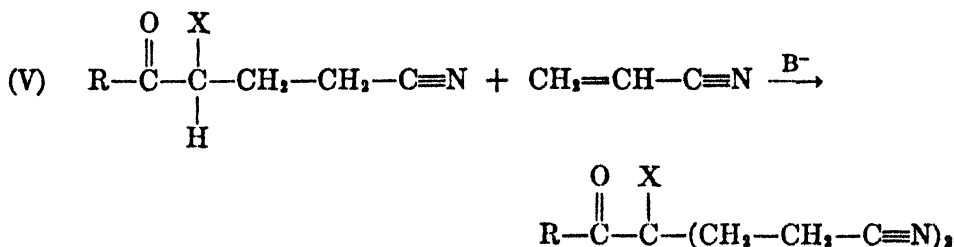
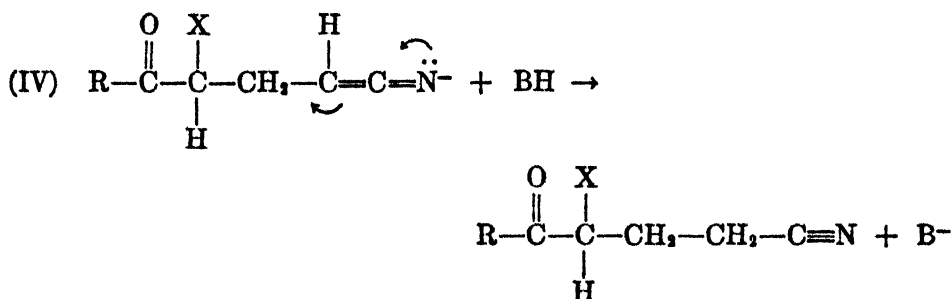


TABLE I
CYANOETHYLATION PRODUCTS OF CERTAIN METHYL KETONES

KETONE	PRODUCT	M.P. °C.	YIELD, %	
			BTAB	Triton B
2-Acetylthiophene	1,1,1-tri-(2-cyanoethyl)methyl 2-thienyl ketone	145-146	89	87.7 (4)
2-Acetylfuran	1,1,1-tri-(2-cyanoethyl)methyl 2-furyl ketone	120-121	90	89.2 (4)
Acetophenone	1,1,1-tri-(2-cyanoethyl)acetophenone	127-128	64	57 (1)

In equation (I) the base reacts with the active hydrogen compound and converts it partially to its anion. Equation (II) shows two of the resonance forms of acrylonitrile. The anion of the active hydrogen compound then condenses with the active form of acrylonitrile (equation III) to produce the anion of the condensation product, which then (equation IV) picks up a proton from BH (equation I) to produce the monocyanoethylated product and regenerate the base. If the active hydrogen compound is a β -diketone or a β -keto ester containing two hydrogen atoms on a methylene carbon atom, the series of reactions is repeated to produce the dicyanoethylated product. In the case of the methyl ketones studied (*e.g.*, 2-acetylthiophene) all three of the active hydrogen atoms are replaced by cyanoethyl groups.

In Table I are found the yields of the tricyanoethylated products of 2-acetylthiophene, 2-acetylfuran, and acetophenone prepared in this investigation using BTAB as the condensing agent. It can be seen that the yields compare favorably with those obtained by Bruson and Riener (1, 4). In Table II are found the

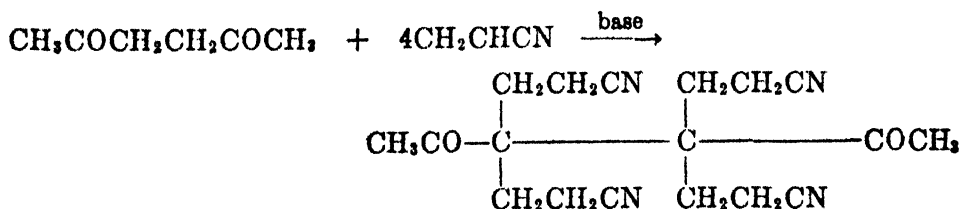
yields of the cyanoethylated derivatives of a number of β -keto esters and β -diketones. It will be observed that the yields of the products are fair to good in all cases. In those cases where both Triton B and BTAB were used as the condensing agents, the yields of the cyanoethylation products are about the same, within experimental error.

One 1,4-diketone (acetonylacetone) was also cyanoethylated. Although the structure of the compound has not yet been definitely proven, its analysis indi-

TABLE II
CYANOETHYLATION PRODUCTS OF CERTAIN β -KETO ESTERS AND DIKETONES

ACTIVE HYDROGEN COMPOUND	PRODUCT	YIELD, %		M.P. °C.	N ANALYSIS	
		Triton B	BTAB		Calc'd	Found
Ethyl acetoacetate	Ethyl 2,2-di-(2-cyanoethyl)-3-ketobutanoate	79	80	81 - 81.5 (1)		
Ethyl <i>n</i> -butyrylacetate	Ethyl 2,2-di-(2-cyanoethyl)-3-ketohexanoate	34	36	40.3- 41.5	10.60	10.87
Ethyl isovalerylacetate	Ethyl 2,2-di-(2-cyanoethyl)-3-keto-5-methylhexanoate	65	68	53.5- 54.4	10.06	10.18
Ethyl benzoylacetate	Ethyl 2,2-di-(2-cyanoethyl)-2-benzoylethanoate	53		61.5- 62	9.39	9.19
Ethyl 2-thenoylacetate	Ethyl 2,2-di-(2-cyanoethyl)-2-(2-thenoyl)ethanoate	32		100.5-101	9.21	9.13
Ethyl 2-furoylacetate	Ethyl 2,2-di-(2-cyanoethyl)-2-(2-furoyl)ethanoate	25		91 - 91.5	9.73	10.01
Acetylacetone	3,3-Di-(2-cyanoethyl)-2,4-pentanedione	49	55	180 -180.4	13.58	13.30
Acetylbenzoylmethane	1-Benzoyl-1,1-di-(2-cyanoethyl)propanone	22		107 -107.2	10.44	10.53
Acetyl-2-thenoylmethane	1-(2-Thenoyl)-1,1-di-(2-cyanoethyl)propanone	40		127 -127.5	10.21	10.12
Acetonylacetone	3,3,4,4-Tetra-(2-cyanoethyl)-2,5-hexanedione	46	50	179 -179.5	17.46	17.29

cates the presence of four cyanoethyl groups. It is probably 3,3,4,4-tetra-(2-cyanoethyl)-2,5-hexanedione produced according to the following equation.



Some support for believing that the cyanoethyl groups were introduced on the methylene carbon atoms may be obtained from the work of Bruson and Riener

(1). They have shown that ketones which have the grouping, $-\text{CH}_2\text{COCH}_3$, are primarily cyanoethylated at the methylene carbon atom. This tetra-cyanoethylated derivative of acetonylacetone was prepared earlier by Bruson (9).

EXPERIMENTAL

Starting Materials

Triton B and benzyltrimethylammonium butoxide. These compounds were generously supplied by the Rohm and Haas Company, Philadelphia, Pa.

Acetonylacetone. This diketone supplied by the Carbide and Carbon Corp., Charleston, W. Va.

2-Acetylthiophene. This ketone was purchased from the Socony-Vacuum Oil Co., Paulsboro, N. J.

2-Acetylfulan. This ketone was prepared by the method of Heid and Levine (5).

All the β -keto esters, with the exception of ethyl acetoacetate, which was purchased from the Eastman Kodak Co., and the β -diketones used in this investigation, were prepared by methods already described in the literature (6, 7, 8).

Preparation of cyanoethylated β -keto esters. The apparatus used in these reactions consists of a 500-ml. three-necked round-bottomed flask equipped with ground-glass joints, a mercury-sealed stirrer, a reflux condenser, and an addition funnel. To the rapidly stirred solution of 0.1 mole of the β -keto ester, 0.2 mole of *t*-butyl alcohol and 3 g. of Triton B or 5 g. of BTAB, 0.2 mole of acrylonitrile is added slowly over a period of 20 minutes. The temperature of the reaction mixture is kept near room temperature by occasionally immersing the flask in an ice-water bath. The reaction mixture is stirred for two hours after the addition of the acrylonitrile is complete. The contents of the flask is then poured into ice-water. In those cases where a solid is formed at this point, it is filtered on a Büchner. In those cases where a solid does not form in ice-water, the reaction mixture is extracted with ether. The ethereal solution is dried over Drierite, the ether distilled, and the *t*-butyl alcohol removed in a vacuum. The remaining viscous liquid is dissolved in cold acetone or ethyl alcohol and allowed to crystallize. Usually at this point a tarry mass is obtained. The tar is washed out by adding more acetone or alcohol, leaving behind the cyanoethylated β -keto ester. The crystalline residue is recrystallized from ethyl alcohol. The cyanoethylated β -keto esters prepared are found in Table II.

Preparation of cyanoethylated diketones. The apparatus used is the same as that described above. The proportions of reactants are also the same as described above except in the case of acetonylacetone, in which 0.4 mole of nitrile was used for 0.1 mole of the diketone. The rapidly stirred solution of the diketone, *t*-butyl alcohol, and base is warmed to 40°, and the acrylonitrile added slowly. After the addition of the acrylonitrile is complete, the solution is stirred and refluxed gently for two hours longer. The products are then isolated as described above.

Preparation of cyanoethylated ketones. The procedure used is the same as that described by Bruson and Riener (4) except that BTAB is used as the base instead of Triton B. The compounds prepared are found in Table I.

SUMMARY

A number of β -keto esters, β -diketones, and one γ -diketone have been cyanoethylated in fair to good yields.

Three methyl ketones have been cyanoethylated using BTAB as the condensing agent. The yields of the compounds compare satisfactorily with those obtained earlier in the presence of Triton B.

PITTSBURGH, PA.

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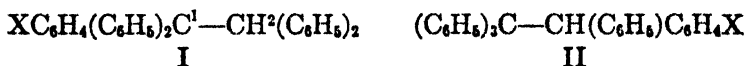
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THE EFFECT OF HALOGEN ATOMS AND OF ALKYL GROUPS ON THE RATES OF DISSOCIATION OF PENTAARYLETHANES

W. E. BACHMANN, E. CARLSON, JR.¹, AND J. C. MORAN²

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In order to determine the effect of chlorine and bromine atoms on the rates of dissociation of pentaarylethanes, the following compounds I and II (X = Cl or Br in the *o*-, *m*-, and *p*-positions) were prepared. In I the halogen is on the



triphenylmethyl group (whose central carbon atom is labelled C-1); in II the halogen is on the diphenylmethyl group (central carbon, C-2). The rates of dissociation of these compounds at 80° were determined by the reaction with iodine (1). The rate constants for the unimolecular reactions and the half-life periods in minutes are shown in Table I. Included for comparison are the results obtained previously with compounds of type II (X = F) showing the effect of the fluorine atom in the *o*-, *m*-, and *p*-positions on a phenyl group on C-2 (diphenylmethyl carbon) (2).

Substitution of a chlorine or bromine atom in the *ortho* position of one of the three phenyl rings on C-1 markedly increased the rate of dissociation; the bromine atom had a greater effect than the chlorine atom. Indeed, the rate of dissociation of the bromo compound (1-*o*-bromophenyl-1,1,2,2-tetraphenylethane) was too great (half-life periods of 1.4–1.8 minutes were indicated) for accurate measurement at 80°; accordingly the rate was measured at a lower temperature (52.6°) and the value at 80° was calculated with the aid of the Arrhenius equation employing the value 27.1 kcal. for the heat of activation (1). The presence of a chlorine or bromine atom in the *m*- and *p*-positions of a phenyl group on C-1 had practically no effect.

Substitution of chlorine or bromine in the *o*-position of one of the two phenyl groups on C-2 had no effect on the rate of dissociation. These results are in marked contrast to the effects of the *o*-methyl ($t_{1/2}$ = 22 min.) and the *o*-methoxy ($t_{1/2}$ = 20 min.) groups in the same positions. Clearly, this indicates that the steric effect is not the only effect operating, for the bromine atom is considered to have about the same size as the methyl group (3). Substitution in the *m*- or *p*-positions decreased somewhat the rate of dissociation. It will be of interest to determine the effect of other electron-attracting groups.

Eight alkyl groups (methyl, ethyl, two propyl, three butyl, and the cyclohexyl groups) were introduced in the para position of compounds of type I and II

¹ The material on the halogenated pentaphenylethanes is from the Ph.D. dissertation of Elmer Carlson Jr., 1943 (present address: Shell Chemical Co., Long Beach, California).

² The material on the *p*-alkylpentaphenylethanes is from the Ph.D. dissertation of James C. Moran, 1943 (present address: General Aniline Works, Grasselli, New Jersey).

(X = *p*-alkyl group) and the rates of dissociation of the compounds were determined. The results are shown in Table II. Although the effect of the alkyl groups is not great, the trend is toward increase in the rate of dissociation; in general the effect is more pronounced the greater the size of the group and the more extensive the branching of the chain, the greatest effect being observed with the *tert*.-butyl and cyclohexyl groups. The effects of the *p*-alkyl groups are greater when situated on a phenyl group attached to C-2; the half-life periods of the compounds II (X = *p*-alkyl) are about 20% less than those of the compounds I (X = *p*-alkyl).

TABLE I
RATE CONSTANTS AND HALF-LIFE PERIODS OF MONOHALOGENATED
PENTAPHENYLETHANES AT 80°
Pentaphenylethane: $t_{1/2} = 56$ min.

POSITION OF HALOGEN ^a	HALOGEN		
	F	Cl	Br
	$t_{1/2}$ (h)	$t_{1/2}$ (h)	$t_{1/2}$ (h)
1- <i>o</i> -		13 (0.0548)	1.65 (0.420) ^b
1- <i>m</i> -		54 (0.0128)	55 (0.0125)
1- <i>p</i> -		56 (0.0124)	52 (0.0133)
2- <i>o</i> -	63 (0.0110) ^c	56 (0.0123)	55 (0.0127)
2- <i>m</i> -	54 (0.0128) ^c	65 (0.0107)	67 (0.0104)
2- <i>p</i> -	67 (0.0104) ^c	68 (0.0101)	63 (0.0110)

^a The number 1 or 2 indicates that the halogen atom is on the triphenylmethyl group, 1, or on the diphenylmethyl group, 2.

^b Calculated from the value observed at 52.6° where $k = 0.0188$ and $t_{1/2} = 37$ min.

^c Determined by Bachmann, Hoffman, and Whitehead (2).

EXPERIMENTAL

Pentaphenylethanes containing a Halogen Atom

o-Chlorobenzohydrol. To an ice-cold solution of the Grignard reagent prepared from 20 g. of bromobenzene in 50 cc. of ether 17.8 g. of *o*-chlorobenzaldehyde was added dropwise over a period of forty-five minutes. The mixture was then hydrolyzed with ice-cold ammonium chloride solution containing some hydrochloric acid; yield, 14.3 g. (52%); m.p. 65–66° [reported (4), 65°].

In another method a mixture of 5 g. of *o*-chlorobenzophenone (5), 7 g. of aluminum isopropoxide, and 15 cc. of isopropyl alcohol was refluxed for two hours and then distilled slowly over a period of one hour (negative acetone test after twenty minutes). The hydrol was recrystallized from petroleum ether; yield, 4.5 g. (95%); m.p. 61–64°.

m-Chlorobenzohydrol. On addition of 14.1 g. of freshly distilled benzaldehyde dropwise in the course of an hour to the ice-cold Grignard reagent from 31.6 g. of *m*-chloriodobenzene in 50 cc. of ether, the addition complex separated as a solid. The solid was collected on a filter, washed with cold ether, and hydrolyzed with ice-cold ammonium chloride solution. The carbinol, which was isolated with ether, was obtained crystalline by chilling a benzene-petroleum ether solution in an alcohol-Dry Ice-bath; yield, 14.4 g. (49%); m.p. 38–40° [reported (6), 41°].

p-Chlorobenzohydrol. This hydrol was obtained by reduction of 15 g. of *p*-chlorobenzo-

phenone (5) with a solution of 30 g. of aluminum isopropoxide in 150 cc. of isopropyl alcohol; yield, 14 g. (92%); m.p. 59–61° [reported (7), 57–59°].

o-Bromobenzohydrol. *o*-Bromobenzophenone (14.8 g.), m.p. 35°, prepared from *o*-bromobenzoyl chloride by the Friedel-Crafts reaction, was reduced by 15.5 g. of aluminum isopropoxide in 75 cc. of dry benzene; yield, 8.9 g. (60%); m.p. 48–50°.

m-Bromobenzohydrol. *m*-Bromobenzonitrile was obtained in 54% yield from *m*-bromoaniline by the procedure described for *o*-tolunitrile in *Organic Syntheses* (8). A solution of 4.6 g. of the nitrile in 25 cc. of dry benzene was added to an ice-cold solution of the Grignard reagent prepared from 19 g. of bromobenzene in 65 cc. of ether. After being stirred for one hour at room temperature, the mixture was refluxed for four hours, and then allowed to stand at room temperature for twelve hours. The addition product was hydrolyzed with ice-cold ammonium chloride solution, the aqueous layer was extracted with two 50-cc. portions of benzene, and the combined ether-benzene solution was concentrated by evaporation in a current of air and dried with magnesium sulfate. Dry hydrogen chloride was passed into the solution for two hours, and the crystalline phenyl *m*-bromophenyl ketimine hydrochloride (6.3 g.) which precipitated was filtered and heated with 100 cc. of 10% hydrochloric acid on a steam-bath for four hours. The resulting *m*-bromobenzophenone crystallized from alcohol in needles; yield, 4.6 g. (86%); m.p. 74–77° [reported (4), 77°].

TABLE II

RATE CONSTANTS AND HALF-LIFE PERIODS OF *p*-ALKYLPENTAPHENYLETHANES AT 80°

ALKYL GROUP	POSITION OF <i>p</i> -ALKYL GROUP	
	1-Carbon $t_{1/2}$ (h)	2-Carbon $t_{1/2}$ (h)
<i>p</i> -Methyl.....	55 (0.0125)	53 (0.0131)*
<i>p</i> -Ethyl.....	51 (0.0135)	43 (0.0161)
<i>p</i> - <i>n</i> -Propyl.....	53 (0.0131)	43 (0.0161)
<i>p</i> -Isopropyl.....	48 (0.0145)	39 (0.0177)
<i>p</i> - <i>n</i> -Butyl.....	51 (0.0137)	40 (0.0172)
<i>p</i> - <i>sec</i> -Butyl.....	49 (0.0141)	39 (0.0179)
<i>p</i> - <i>tert</i> -Butyl.....	46 (0.0149)	37 (0.0186)
<i>p</i> -Cyclohexyl.....	45 (0.0152)	36 (0.0191)

* Determined by Bachmann and Osborn (1).

Reduction of the ketone by 2% sodium amalgam and alcohol in ether and benzene according to the procedure of Bachmann (9) yielded the hydrol as a liquid which crystallized on cooling but melted when warmed to room temperature [reported (10), m.p. 43°]. The hydrol obtained by reduction of 7.5 g. of the ketone with 15 g. of aluminum isopropoxide in 15 cc. of dry benzene failed to crystallize.

p-Bromobenzohydrol. *p*-Bromobenzophenone (m.p. 81–82°) was prepared from *p*-bromobenzoyl chloride and benzene by the Friedel and Crafts reaction (11); it was also made from *p*-bromobenzonitrile (18.4 g.) and four equivalents of phenylmagnesium bromide according to the procedure described for the *meta* isomer; yield, 19 g. (90%); m.p. 79–81.5°. After recrystallization from petroleum ether it melted at 81–82°. Reduction of 13.5 g. of the ketone with 21 g. of aluminum isopropoxide in 105 cc. of benzene gave 11.6 g. (86%) of *p*-bromobenzohydrol; m.p. 63–65° [reported (12), 63.5°].

Preparation of the halogenated benzohydryl halides. *o*-Bromo- and *p*-chloro-benzohydryl chloride were prepared from the hydrols and hydrogen chloride by the procedure employed by Bateman, Hughes, and Ingold (6). *o*-Chloro-, *m*-chloro-, *m*-bromo-, and *p*-bromobenzohydryl bromide were prepared by warming a mixture of 5 g. of the hydrol, 10 cc. of benzene, and 10 cc. of acetyl bromide on a steam-bath for one hour. After being freed of acetic acid and excess acetyl bromide by evaporation at room temperature in a high vacuum, the halides were used without further purification in the coupling reaction.

Preparation of the pentaarylethanes containing a halogen atom. The 1-aryl-1,1,2,2-tetraphenylethanes (with a halogen atom in the aryl group) were prepared by shaking a solution of the monohalogenotriphenylchloromethane (13) and diphenylbromomethane in ether-benzene with mercury (14). Considerable difficulty was encountered in the preparation of 1-*o*-bromophenyl-1,1,2,2-tetraphenylethane, which has the highest rate of dissociation. The compound was successfully prepared only when all operations (reaction, filtration, concentration, and recrystallization) were carried out in a nitrogen atmosphere; these operations were performed in a Gomberg free radical bulb (15).

The 1,1,1,2-tetraphenyl-2-arylethanes were prepared by reaction of triphenylmethyl-sodium with the halogenated benzohydril halides in ether-benzene by the procedure of Bachmann and Wiselogle (14).

TABLE III
YIELDS AND PROPERTIES OF 1-ARYL-1,1,2,2-TETRAPHENYLETHANES AND OF 1,1,1,2-TETRAPHENYL-2-ARYLETHANES CONTAINING A HALOGEN ATOM

HALOGEN ATOM ON ARYL GROUP	POSITION OF ARYL GROUP	YIELD, %	CRYST FORM	M.P. (IN VAC.), °C.	ANAL. FOR HALOGEN	
					Calc'd	Found
<i>o</i> -Chloro-	1	21	Fine needles	157-158	7.97	7.97
	2	81	Platelets	180-182		7.99
<i>m</i> -Chloro-	1	70	Powder	157-158		8.40
	2	70	Plates	167-168.5		7.95
<i>p</i> -Chloro-	1	74	Long prisms	170-171		8.13
	2	44	Powder	163-164.5		8.13
<i>o</i> -Bromo-	1	68	Fine needles	159-160	16.31	15.88
	2	61	Plates	184-186		15.50
<i>m</i> -Bromo-	1	88	Powder	158-161		15.78
	2	60	Plates	165-167		15.85
<i>p</i> -Bromo-	1	76	Plates	167-169		15.72
	2	—	Powder	158.5-161		16.89

All of the pentaarylethanes are colorless. All were recrystallized from a mixture of benzene-petroleum ether except the *o*-chloro- and *m*-chloro- compounds for which a mixture of chloroform and alcohol was employed. The compounds were held at 60-80° and 0.01 mm. for six to twenty-four hours in order to remove the solvents which were held tenaciously. The low values for bromine may be attributed to the difficulty of removing the solvent completely without decomposing the compounds. The results are shown in Table III.

Monoalkylpentaphenylethanes

p-Alkylbenzophenones. Five of these ketones were prepared from the *p*-alkylbenzene and benzoyl chloride by the Friedel and Crafts reaction. The ketones which were not obtained crystalline may have contained some of the isomers which were not removed by distillation. In several instances crystalline hydrols were obtained.

p-Ethylbenzophenone has been prepared by several investigators; recently it was obtained in 55% yield by adding ethylbenzene to the other reagents (16). We obtained the ketone by adding 15 g. of benzoyl chloride dropwise over a two-hour period to a cold mixture of 30 g. of ethylbenzene, 20 cc. of carbon disulfide, and 15 g. of aluminum chloride, and

allowing the mixture to stand at room temperature until evolution of hydrogen chloride ceased; yield, 18.5 g.; b.p. 144°/0.2 mm.; 315°/730 mm.

The same procedure was used to prepare *p*-*n*-propylbenzophenone (49.5 g.; b.p. 114°/0.05 mm.) from *n*-propylbenzene (38 g., prepared by Clemmensen reduction of propiophenone) and benzoyl chloride (44 g.). Similarly, *p*-*n*-butylbenzophenone was prepared from 47 g. of *n*-butylbenzene and 57 g. of benzoyl chloride; yield, 68.5 g.; b.p. 164°/0.65 mm.

Anal. Calc'd for $C_{17}H_{15}O$: C, 85.7; H, 6.7.

Found: C, 86.1; H, 6.9.

p-*tert*-Butylbenzophenone was obtained in crystalline form from 16 g. of *tert*-butylbenzene (17) and 25 g. of benzoyl chloride in carbon disulfide; yield, 21 g. (74%); m.p. 36–37.5° [reported (20) as liquid, b.p. 205°/15 mm.]. Cyclohexylbenzene (80 g.), prepared from cyclohexyl chloride (18) and benzene according to the procedure of Kursanoff (19), was allowed to react with benzoyl chloride (70 g.) in the presence of aluminum chloride (70 g.); yield, 64 g.; b.p. 167°/0.2 mm.; m.p. 47°. After recrystallization from petroleum ether it melted at 48°. Kleene (20) obtained a product melting at 59–60° by essentially the same procedure. Our ketone gave an oxime with m.p. 124–126° in agreement with the value, 125–127°, reported by Kleene.

p-Isopropyl- and *p*-*sec*-butylbenzophenone were prepared by the Grignard reaction. A mixture of 25 g. of benzonitrile, 25 cc. of benzene and the Grignard reagent from 40 g. of *p*-isopropylbromobenzene (prepared by bromination of cumene) was refluxed for twelve hours, and the resulting ketimine was isolated as the hydrochloride and hydrolyzed; yield, 20 g.; b.p. 116–118°/0.04 mm. From 10.3 g. of benzonitrile and 21 g. of *p*-*sec*-butylbromobenzene (21), 12 g. (50%) of *p*-*sec*-butylbenzophenone was obtained; b.p. 137–139°/0.04 mm.

p-Alkylbenzohydrols. *p*-*sec*-Butylbenzohydrol was obtained as a liquid by slow distillation of a mixture of 8 g. of the ketone, 21 g. of aluminum isopropoxide, and 125 cc. of benzene until no more acetone appeared (four hours). The other hydrols were prepared by reducing the ketones by the method of Bachmann (9). Thus, a mixture of 18 g. of *p*-ethylbenzophenone, 100 cc. of anhydrous ether, 100 cc. of dry benzene, 10 cc. of absolute alcohol, and 245 g. of 2% sodium amalgam was shaken in a strong bottle until the brilliant blue ketyl color was replaced by a green color (thirty minutes); yield, 10 g. (55%); m.p. 42–42.5° [recently reported in 75% yield by zinc and alcoholic alkali solution (16); m.p. 43.5°]. *p*-Isopropylbenzohydrol (m.p. 57–59°) was obtained in 51% yield; after recrystallization from petroleum ether it melted at 59–60° [reported (16), 59–60°]. *p*-*n*-Propyl- and *p*-*n*-butylbenzohydrol were not obtained crystalline. From 17 g. of *p*-*tert*-butylbenzophenone 16.7 g. of the hydrol was obtained; after recrystallization from petroleum ether it melted at 81.5–82° [reported (16), 82°]. From 21.6 g. of the ketone 19.3 g. of *p*-cyclohexylbenzohydrol was obtained; m.p. 74.5–74.7° after recrystallization from ligroin.

Anal. Calc'd for $C_{10}H_{12}O$: C, 85.65; H, 8.31.

Found: C, 85.53; H, 8.39.

p-Alkylbenzohydryl halides. In all but one instance the chlorides were prepared; these were made by refluxing a mixture of 10–20 g. of the hydrol with 10–20 cc. of acetyl chloride on a steam-bath for one-half hour and distilling the product under reduced pressure. From 9.6 g. of *p*-ethylbenzohydrol 5.8 g. (56%) of the chloride boiling at 185–190°/17 mm. was obtained; the chloride had been made previously by means of hydrogen chloride (16).

From 20 g. of the hydrol 16.3 g. (74%) of *p*-*n*-propylbenzohydryl chloride was obtained; b.p. 122–124°/0.1 mm.

Anal. Calc'd for $C_{10}H_{11}Cl$: Cl, 14.5. Found: Cl, 14.31.

The *p*-isopropylbenzohydryl chloride (2 g. from 2.6 g. of hydrol) boiled at 116°/0.05 mm.; it had been made previously by means of hydrogen chloride (16).

From 25 g. of the hydrol 26 g. of *p*-*n*-butylbenzohydryl chloride was obtained; b.p. 179°/11 mm.

Anal. Calc'd for $C_{12}H_{13}Cl$: Cl, 13.7. Found: Cl, 13.5.

p-*sec*-Butylbenzohydryl bromide was prepared from the hydrol (8 g.) and excess acetyl bromide; yield, 9 g. (88%); b.p. 151–154°/0.5 mm.

Anal. Calc'd for $C_{17}H_{19}Br$: Br, 26.4. Found: Br, 26.1.

From 6 g. of *p-tert.*-butylbenzohydrol 5.4 g. of the chloride [previously prepared by means of hydrogen chloride (16)] was obtained.

p-Cyclohexylbenzohydrol chloride was obtained in nearly quantitative yield; after recrystallization from petroleum ether the chloride melted at 64–66°.

Anal. Calc'd for $C_{13}H_{21}Cl$: Cl, 12.46. Found: Cl, 12.31.

Preparation of p-alkyltriphenylchloromethanes. The *p*-alkylbenzophenones were converted into *p*-alkyltriphenylcarbinols by reaction with phenylmagnesium bromide in the

TABLE IV
YIELDS AND PROPERTIES OF 1-ARYL-1,1,2,2-TETRAPHENYLETHANES AND 1,1,1,2-TETRAPHENYL-2-ARYLETHANES CONTAINING AN ALKYL GROUP

ALKYL GROUP	POSITION OF ARYL GROUP	YIELD, %	M.P. (IN VAC.), °C.	ANALYSES			
				Calc'd		Found	
				C	H	C	H
<i>p</i> -Methyl-	1*	28	163–164	93.35	6.65	92.96	6.67
<i>p</i> -Ethyl-	1	22	145–147	93.10	6.90	92.77	7.15
	2	36	142–144			92.88	7.29
<i>p-n</i> -Propyl-	1	71	155–156	92.87	7.13	92.51	7.20
	2	61	132–134			92.83	7.29
<i>p</i> -Isopropyl-	1	54	161.5–163	92.87	7.13	92.63	7.09
	2	58	158–160			93.11	7.06
<i>p-n</i> -Butyl-	1	23	146.5–147	92.65	7.35	92.33	7.30
	2	48	142–142.5			92.18	7.25
<i>p-sec</i> -Butyl-	1	86	137–141	92.65	7.35	92.49	7.35
	2	84	133.5–135			92.49	7.35
<i>p-tert</i> -Butyl-	1	58	172.5–173	92.65	7.35	92.62	7.49
	2	62	159.5–160			92.33	7.30
<i>p</i> -Cyclohexyl-	1	55	151–153	92.63	7.37	93.00	7.27
	2	70	187–188			92.54	7.56

* 1,1,1,2-Tetraphenyl-2-*p*-tolylethane which has the *p*-methyl group on the aryl group attached to C 2 has been prepared previously (1).

usual manner; biphenyl was removed by steam distillation. All but two (*p* methyl- and *p*-cyclohexyl-) of the carbinols were obtained as liquids and were used without further purification in the next step, which consisted in reaction with acetyl chloride on a steam-bath for one-half hour to form the chloride, followed by removal of the acetic acid and excess acetyl chloride under reduced pressure. *p*-Methyltriphenylchloromethane (22) and *p-tert.*-butyltriphenylchloromethane were prepared from the carbinols with hydrogen chloride in the presence of calcium chloride.

p-Ethyltriphenylchloromethane (6.8 g. from 6.2 g. of ketone) was obtained as an oil. *p-n*-Propyltriphenylchloromethane (33% yield from the ketone) crystallized from the reaction mixture on cooling; after recrystallization from petroleum ether it melted at 90°

in agreement with the value reported for the compound prepared from *p*-*n*-propylbromobenzene and benzophenone (23). *p*-Isopropyltriphenylchloromethane (68% yield from the ketone) crystallized from petroleum ether with the m.p. 90–91° [reported (24), 90–91°].

p-*n*-Butyltriphenylchloromethane could not be obtained crystalline.

Anal. Calc'd for $C_{23}H_{23}Cl$: Cl, 10.6. Found: Cl, 10.1.

p-*sec*.-Butyltriphenylchloromethane (50% yield from the ketone) crystallized from petroleum ether with the m.p. 83–84° in agreement with that reported (23). From 13 g. of *p*-*tert*.-butylbenzophenone 8 g. of *p*-*tert*.-butyltriphenylchloromethane was obtained after recrystallization from petroleum ether; m.p. 134–134.5° in agreement with the value, 133–134°, reported for the product prepared from *p*-*tert*.-butylphenylmagnesium bromide and benzophenone (24). An 86% yield of *p*-cyclohexyltriphenylchloromethane with m.p. 125–126° was obtained in agreement with Marvel and Himel (25).

Preparation of the monoalkylpentaphenylethanes. Three of the pentaarylethanes (1-*p*-ethylphenyl- and 1-*p*-*sec*.-butylphenyl-1,1,2,2-tetraphenylethane and 1,1,1,2-tetraphenyl-2-*p*-*sec*.-butylphenylethane) were prepared by the mercury coupling reaction (four days of shaking in ether-benzene); the others were prepared from triphenylmethylsodium (or *p*-alkyltriphenylmethylsodium) and the *p*-alkylbenzohydryl halide (or benzohydryl bromide). Most of the pentaarylethanes were recrystallized from a mixture of chloroform and alcohol and dried to constant weight at 60–80° in a high vacuum. The results are shown in Table IV.

SUMMARY

Twelve pentaphenylethanes containing a chlorine or bromine atom in the *o*-, *m*-, and *p*-positions of a phenyl group and fifteen mono-*p*-alkylpentaphenylethanes were synthesized, and their rates of dissociation at 80° were measured by the rate at which iodine was absorbed.

The rate of dissociation was increased markedly by a chlorine or bromine atom in the *ortho* position of a phenyl group attached to the triphenylmethyl carbon; a slight decrease in the rate resulted when a halogen atom was in the *meta* or *para* position of a phenyl group attached to the diphenylmethyl carbon.

All of the alkyl groups increased the rate of dissociation, the greatest effect being obtained when the group was on a phenyl group attached to the diphenylmethyl carbon atom.

ANN ARBOR, MICHIGAN

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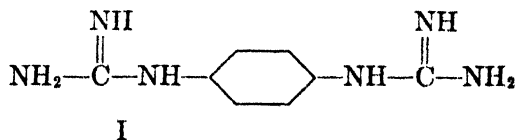
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EXPERIMENTAL CHEMOTHERAPY OF TRYPANOSOMIASIS. II. THE PREPARATION OF COMPOUNDS RELATED TO *p*-PHENYLENEDIGUANIDINE

S. R. SAFIR, S. KUSHNER, L. M. BRANCONE, AND Y. SUBBAROW

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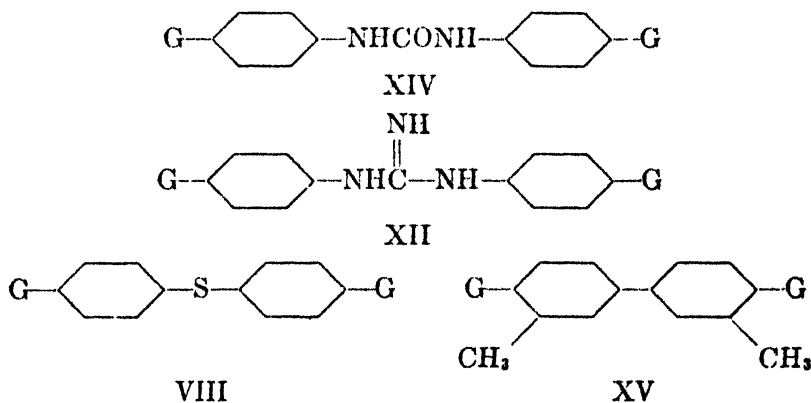
Investigations in our laboratories have shown that *p*-phenylenediguanidine (I) (1) possesses curative properties against *Trypanosoma equiperdum* in mice



(2). A program was therefore undertaken to synthesize compounds structurally related to I.

The meta analog of I was prepared and found to be inactive. The substitution of a chlorine atom or methyl group into the nucleus of I caused a sharp fall in activity. Similarly, alkyl or aryl substitution on the terminal nitrogen atoms resulted in a loss of activity.

By linking the two guanidine groups with bridges other than the *p*-phenylene group it was found that active compounds resulted. The following guanidine derivatives are about as active as I:



Compounds which contained only one guanidine group per molecule invariably possessed little or no trypanocidal activity. This result parallels the observation of King, Laurie, and York (3) that while the polymethylene

diguanidines $\text{NH}_2-\overset{\text{NH}}{\underset{\parallel}{\text{C}}}-\text{NH}(\text{CH}_2)_{10-14}-\text{NH}-\overset{\text{NH}}{\underset{\parallel}{\text{C}}}-\text{NH}_2$ are active trypanocides, the corresponding alkyl guanidines are without effect.

Several biguanide analogs of I and of other guanidines were prepared but these were inactive or weakly active.

A number of guanidine derivatives of basic fuchsin were prepared in the hope of augmenting the well-known trypanocidal activity of the fuchsin dyes. The products were about as active as the parent dyestuffs, but because of high toxicity they were not exploited further.

The complete results of the parasitological tests are reported elsewhere (2).

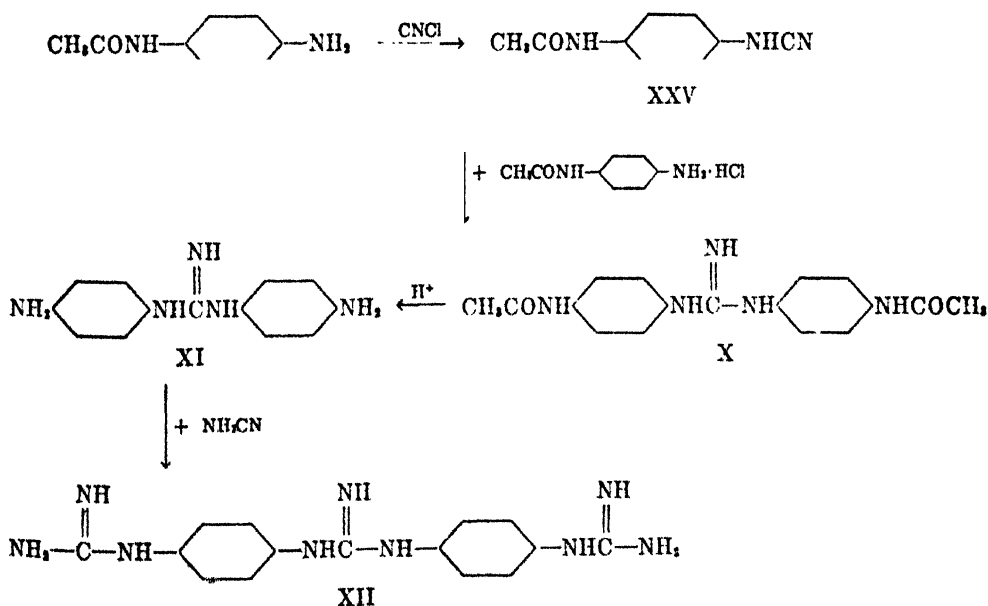
The guanidines were prepared by several procedures. The *p,p'*-monosubstituted diguanidines were made from the corresponding aromatic diamines, in the form of the hydrochloride salts, and cyanamide in alcohol (4, 5). The products were isolated as the free bases or carbonate salts or as the neutral hydrochlorides or picrates.

In the case of *p*-aminobenzylamine hydrochloride, reaction with cyanamide in alcohol or water gave only a monoguanidine derivative. The guanidino group is assumed to be attached to the benzene ring inasmuch as benzylamine hydrochloride fails to react with cyanamide under these conditions, while aniline hydrochloride yields phenylguanidine readily (5).

On the other hand, *p*-aminobenzylamine reacts with methylisothiourea sulfate to yield an isomeric monoguanidino derivative in which the guanidino group is probably attached to the side-chain methyl group. It was found possible to introduce a second guanidino group by treating *p*-guanidinobenzylamine dihydrochloride with slightly more than one equivalent of dilute alkali and then reacting with aqueous cyanamide.

The 1,6-diisopropyl-, dilauryl- and diphenyl-*p*-phenylenediguanidines were prepared by fusion of the requisite cyanamides with *p*-phenylenediamine dihydrochloride.

1,3-Bis-(*p*-guanidinophenyl)guanidine (XII) was prepared according to the following sequence of reactions:



The biguanide derivatives were prepared from the amine hydrochlorides and dicyandiamide either by fusion (6) or in aqueous solution (7). In the case of *p*-aminobenzyl amine, only one biguanido group formed, presumably from the aromatic amino group.

In Table I are listed the various guanidine and biguanide derivatives, together with melting point data and yields.

Acknowledgment. The authors are grateful to Miss Barbara Eames and Messrs. Philip Weiss, William Fulmor, Samuel S. Modes and Oscar Dike for the microanalyses.

EXPERIMENTAL

Isopropyl-, dodecyl-, (8) and phenyl-cyanamide (9). These cyanamides were prepared by distillation of one equivalent of cyanogen chloride into an ice-cold solution of two equivalents of the required base in ether or benzene. After filtration of the hydrochloride of the base, the product was recovered by evaporation of the filtrate *in vacuo* at 25°. All three were obtained in high yields as light yellow oils and were used without further purification.

p-Acetamidophenylcyanamide (XXV). Into a stirred slurry of 25 g. of *p*-aminoacetanilide and 8.4 g. of calcium carbonate in 600 cc. of water there was distilled, during one hour, 10.3 g. of cyanogen chloride. After being stored for fifteen hours, the crystalline product was filtered and washed with water; yield 27 g. (91%), m.p. 178–182°. After two recrystallizations from 50% ethanol, the m.p. was 181–184°.

Anal. Calc'd for $C_9H_9N_3O$: N, 24.0. Found: N, 24.1.

3,3'-Diisopropyl-1,1'-(p-phenylene)diguandine (V). A mixture of 2.5 g. of isopropylcyanamide and 2.4 g. of *p*-phenylenediamine dihydrochloride was heated to 105–110° whereupon an exothermic reaction took place. The melt was kept at a bath temperature of 105–110° for three-quarters of an hour, whereupon the contents had almost completely solidified. The product was dissolved in water, treated with Norit and filtered. The filtrate was treated with a large excess of 5 *N* alkali; the free base separated in the form of glistening plates, m.p. 216–218° (dec.); yield 2.1 g. One recrystallization from ethanol raised the m.p. to 223–225° (dec.).

A portion of the base was dissolved in alcoholic hydrochloric acid and excess ether was added. The resulting dihydrochloride, m.p. 289–291°, was then recrystallized three times from alcohol-ether; m.p. 291–293°.

Anal. Calc'd for $C_{14}H_{20}Cl_2N_6$: C, 48.2; H, 7.5; N, 24.0.

Found: C, 47.8; H, 8.1; N, 23.5.

3,3'-Dilauryl-1,1'-(p-phenylene)diguandine (VI). A mixture of 4.2 g. of dodecylcyanamide and 1.8 g. of *p*-phenylenediamine dihydrochloride was heated slowly to 140° whereupon slow fusion took place and the inner temperature rose to 150°. After three-quarters of an hour the mixture was cooled, the sticky material was leached with hot ethanol and filtered from a small amount of phenylenediamine hydrochloride. The alcoholic solution was treated with Norit, filtered and concentrated to 50 cc. About 150 cc. of ether was added and the dihydrochloride settled out as a fine powder, m.p. 240–265°; yield 1.5 g. After two recrystallizations from ethanol, the m.p. was 260–265°.

Anal. Calc'd for $C_{32}H_{42}Cl_2N_6$: N, 14.0. Found: N, 14.1.

3,3'-Diphenyl-1,1'-(p-phenylene)diguandine (VII). This compound was prepared in a similar manner to V. The reaction became exothermic at 120° whereupon the heating bath was removed. The liberated base was recrystallized from ethanol; m.p. 209–211° (dec.). The hydrochloride melted at 253–257° after two recrystallizations from ethanol-ether.

TABLE I
COMPOUNDS RELATED TO *p*-PHENYLENEDIGUANIDINE

COMPOUND	M.P. °C. BASE	M.P. °C. HYDROCHLORIDE	M.P. °C. OTHER SALT	% YIELD
II <i>m</i> -Phenylenediguani- dine			Carbonate gas evolv. at 155; dec. 215	30
III <i>o</i> -Chloro- <i>p</i> -phenylene- diguandine	237-240 (dec.)	302-305 (dec.)		28
IV <i>o</i> -Methyl- <i>p</i> -phenyl- enediguandine	226-229 (dec.)	290-292 (dec.)		36
V 3,3'-Diisopropyl-1,1'- (<i>p</i> -phenylene)diguani- dine	223-225 (dec.)	291-293 (dec.)		58
VI 3,3'-Dilauryl-1,1'-(<i>p</i> - phenylene)diguani- dine		260-265		25
VII 3,3'-Diphenyl-1,1'-(<i>p</i> - phenylene)diguani- dine	200-211 (dec.)	253-257		69
VIII Bis-(4-guanidinophenyl) sulfide (13)			Carbonate 140-146 (dec.)	58
IX Bis-(4-guanidino- phenyl)sulfone		263-265 (dec.)	Picrate 271-273 (dec.)	30
X 1,3-Bis-(<i>p</i> -acetamido- phenyl)guanidine	143-146	303-311 (dec.)		97
XI 1,3-Bis-(<i>p</i> -amino- phenyl)guanidine	204-208 (dec.)	265-275 (dec.)		87
XII 1,3-Bis-(<i>p</i> -guanidino- phenyl)guanidine		292-295		32
XIII 1,3-Bis-(<i>p</i> -ureido- phenyl)guanidine		198-200 (dec.)		67
XIV 1,3-Bis-(<i>p</i> -guanidino- phenyl)urea			Carbonate sinters 135; dec. 148	61
XV 3,3'-Dimethyl-4,4'- diguandinobiphenyl	219-223 (dec.)		Picrate > 270 (dec.)	91
XVI <i>p</i> -Guanidinobenzyl- guanidine			Picrate 250-253 (dec.)	38
XVII <i>p</i> -Guanidinobenzyl- amine	172-176	257-260 (dec.)	Picrate 242-243 (dec.)	63
XVIII <i>p</i> -Aminobenzylguani- dine			Sulfate 195-202 (dec.) Picrate > 197 (dec.)	93
XIX 4,4',4''-Triguanidino- diphenyl-3-tolyl- methane (15)			Carbonate > 330 (dec.)	65
XX 3,3'-Dimethyl-4,4'- diguandinino-4''- aminotriphenylmeth- ane (15)			Carbonate (amor- phous)	76
XXI 4-Aminophenyl-4',4''- diguandinophenyl- tolylmethane (15)			Carbonate (amor- phous)	64
XXII <i>p</i> -Biguanidobenzyl- amine		> 250 (dec.)		44
XXIII <i>p</i> -Phenylenedibiguanide	218-219 (dec.)	270-278 (dec.)		61
XXIV <i>o</i> -Chloro- <i>p</i> -phenylene- dibiguanide	208-210 (dec.)	240-243 (dec.)		54

Anal. Calc'd for $C_{10}H_{22}Cl_2N_4$: N, 20.1. Found: N, 20.2.

2-Chloro-1,4-phenylenediguandine (III). A mixture of 12.9 g. of 2-chloro-1,4-phenylenediamine dihydrochloride, 7.8 g. of cyanamide and 60 cc. of dry ethanol was refluxed two and one-half hours. The mixture was cooled to 5° for several hours and the white crystalline product was filtered; crude yield 5 g., m.p. 294–300° (dec.). A 2-g. portion of the hydrochloride was dissolved in water, the solution was cooled to 5° and an excess of 50% potassium hydroxide was added. The liberated base was filtered and recrystallized from water, separating as hexagonal plates, m.p. 237–240° (dec.); weight 1.1 g. The base was pulverized and triturated with alcoholic hydrochloric acid. The hydrochloride was filtered, washed with ethanol, and recrystallized twice as follows; the solid was suspended in ethanol, the mixture was warmed to 50° and enough water was added to effect solution; after filtration ether was added to the point of persistent turbidity. The dihydrochloride separated in clusters of needles, m.p. 302–305° (dec.).

Anal. Calc'd for $C_8H_{12}Cl_2N_4$: C, 32.0; H, 4.3; N, 28.0.
Found: C, 32.7; H, 4.9; N, 27.9.

2-Methyl-1,4-phenylenediguandine (IV). This compound was prepared in the same manner as III. The base melted at 226–229° (dec.) and the dihydrochloride at 290–292° (dec.).

Anal. Calc'd for $C_9H_{14}Cl_2N_4$: C, 38.7; H, 5.7; N, 30.1.
Found: C, 39.1; H, 6.3; N, 30.4.

m-Phenylenediguandine (II). This compound was made in a similar manner to III. However, a crystalline hydrochloride was not isolated. Instead, the product was converted to the crystalline carbonate which was purified by dissolving in acid and reprecipitating with potassium carbonate; m.p. 215° (dec.), with gas evolution at 155°.

Anal. Calc'd for $C_6H_{12}N_6 \cdot H_2CO_3$: C, 42.5; H, 5.5; N, 33.0.
Found: C, 42.5; H, 4.7; N, 33.3.

4,4'-4"-Triguanidinodiphenyl-3-tolylmethane (XIX) (15). This compound was prepared in a similar manner to II. The product was isolated as the carbonate salt; m.p. 330° (dec.).

Anal. Calc'd for $C_{23}H_{27}N_9 \cdot 1\frac{1}{2}H_2CO_3$: C, 56.3; H, 5.5; N, 24.1.
Found: C, 56.6; H, 5.7; N, 24.2.

3,3'-Dimethyl-4,4'-diguanidino-4"-aminotriphenylmethane (XX)¹ This compound was made from the corresponding triamine trihydrochloride similarly to the preparation of II. The carbonate salt was obtained as an amorphous solid with an indefinite melting point.

Anal. Calc'd for $C_{23}H_{27}N_7 \cdot H_2CO_3$: C, 62.1; H, 6.3.
Found: C, 62.3; H, 7.1.

4-Aminophenyl-4',4"-diguanidinophenyltolylmethane (XXI) (15)¹ This compound was prepared from the triamine trihydrochloride and two equivalents of cyanamide similarly to II. The carbonate salt was obtained as an amorphous solid with an indefinite melting point.

Anal. Calc'd for $C_{22}H_{26}N_7 \cdot H_2CO_3$: C, 61.5; H, 6.1; N, 21.8.
Found: C, 61.5; H, 6.0; N, 20.0.

¹ The exact position of the methyl groups in relation to the guanidino groups is not known.

1,3-Bis-(*p*-guanidinophenyl)urea (XIV). This compound was made from *N,N'*-bis-(4-aminophenyl)urea dihydrochloride (16) by reaction with cyanamide in a similar manner to II. The product was isolated as the carbonate salt, decomposing at 148° with sintering at 135°.

Anal. Calc'd for $C_{15}H_{18}N_8O \cdot H_2CO_3$: C, 49.0; H, 5.2; N, 28.9.
Found: C, 50.3; H, 5.8; N, 27.5.

Bis-(4-aminophenyl)sulfide. This compound has been prepared by Nietzki and Bothof (10) and by Hodgson (11). It may be prepared more conveniently by the reduction of bis-(4-nitrophenyl)sulfide (12) in the following manner: A hot solution of 72.5 g. of stannous chloride dihydrate in 80 cc. of 12 *N* hydrochloric acid was added during one minute to a hot solution of 14 g. of bis-(4-nitrophenyl)sulfide in 150 cc. of acetic acid. After a few minutes the solution was evaporated to dryness *in vacuo*, the crystalline residue was dissolved in water and excess 50% alkali was added. The liberated base was filtered, washed with alkali, then with water and dried; yield 9.8 g. (90%), m.p. 103–106°. The dihydrochloride (13) is formed by dissolving the base in ethanol, adding ethanolic hydrochloric acid and precipitating with ether.

Bis-(4-guanidinophenyl)sulfide (VIII).² A mixture of 6.7 g. of bis-(4-aminophenyl)sulfide dihydrochloride, 3.0 g. of cyanamide, and 45 cc. of ethanol was refluxed five hours, cooled to 25° and treated with four volumes of ether. The resulting gum was triturated several times with ether, dissolved in water, and treated with excess potassium carbonate. The carbonate salt crystallized on rubbing. After one recrystallization from water the yield amounted to 5.0 g.; m.p. 140–146° (dec.).

Anal. Calc'd for $C_{14}H_{16}N_6 \cdot H_2CO_3 \cdot \frac{1}{2}H_2O$: C, 48.6; H, 5.1; N, 22.6.
Found: C, 48.6; H, 5.8; N, 21.6.

Bis-(4-aminophenyl)sulfone dihydrochloride. One hundred grams of bis-(4-aminophenyl)sulfone was dissolved in 200 cc. of water and 80 cc. of 12 *N* hydrochloric acid and excess alcoholic hydrochloric acid was added. The salt was filtered and washed with ethanol; yield 116 g., m.p. 243–248°, (dec.). The hydrochloride dissolves readily in a limited amount of water but on further dilution the free base crystallizes out.

Bis-(4-guanidinophenyl)sulfone (IX). A solution of 12 g. of cyanamide in 40 cc. of ethanol was added during twenty minutes, to a refluxing mixture of 32 g. of bis-(4-aminophenyl)sulfone dihydrochloride and 100 cc. of ethanol. The mixture was then refluxed six hours and filtered from traces of suspended matter. The resulting clear, light brown, neutral solution was treated with excess alcoholic picric acid. After two hours the yellow precipitate was filtered and leached twice with boiling ethanol; m.p. 258–263° (dec.). The yield from a 40-cc. aliquot of the reaction filtrate was 6.3 g. This was suspended in 12 *N* hydrochloric acid. The liberated picric acid was extracted with benzene until a benzene wash failed to give a yellow color when shaken with alkali. The hydrochloric acid solution was evaporated to dryness *in vacuo* and the crystalline dihydrochloride was recrystallized from 90% ethanol and ether. After three recrystallizations the m.p. was 263–265° (dec.).

Anal. Calc'd for $C_{14}H_{14}Cl_2N_6O_2$: C, 41.5; H, 4.4; N, 20.7.
Found: C, 41.3; H, 5.5; N, 21.0.

When an aqueous solution of the purified dihydrochloride was treated with aqueous picric acid, the dipicrate precipitated; m.p. 270–272° (dec.). After one recrystallization from water the m.p. was 271–273° (dec.).

Anal. Calc'd for $C_{24}H_{22}N_{12}O_{16}S$: C, 39.5; H, 2.8; N, 21.3.
Found: C, 39.6; H, 3.2; N, 21.7.

² Braun and Ludwig (13) have prepared this compound and characterized it as the free base, the sulfate, and the picrate.

1,3-Bis-(*p*-acetamidophenyl)guanidine (X). A mixture of 3.5 g. of *p*-acetamidophenylcyanamide, 3.7 g. of *p*-aminoacetanilide hydrochloride, and 125 cc. of chlorobenzene was refluxed two and one-half hours, cooled, and the product was filtered. The yield of crude hydrochloride was 7 g., m.p. 303–311° (dec.).

The hydrochloride is insoluble in alcohol and cold water; it is slightly soluble in hot water and soluble in cold 12 *N* hydrochloric acid.

An aqueous suspension of the hydrochloride was treated with excess alkali. The liberated base was filtered and recrystallized three times from 20% ethanol; m.p. 143–146° (dec.).

Anal. Calc'd for $C_{17}H_{19}N_5O_2$: N, 21.6. Found: N, 20.7.

1,3-Bis-(*p*-aminophenyl)guanidine (XI). A mixture of 14.7 g. of 1,3-bis-(*p*-acetamidophenyl)guanidine and 250 cc. of 12 *N* hydrochloric acid was refluxed forty minutes and then evaporated to dryness *in vacuo*. The crystalline hydrochloride was slurried in ethanol and filtered; yield 12.5 g., m.p. 265–275° (dec.).

It was converted to the base by the addition of alkali. The base was filtered and washed with a little water; m.p. 204–208° (dec.).

Anal. Calc'd for $C_{13}H_{15}N_5 \cdot \frac{1}{2}H_2O$: N, 28.0. Found: N, 28.0.

1,3-Bis-(*p*-guanidinophenyl)guanidine (XII). A mixture of 1.25 g. of the diaminodiphenylguanidine trihydrochloride, 0.46 g. of cyanamide, and 15 cc. of ethanol was refluxed four hours. The mixture was cooled and the hydrochloride of the product was filtered; yield 0.5 g.; m.p. 287–291°. After two recrystallizations from 90% alcohol and ether, the m.p. was 292–295°.

Anal. Calc'd for $C_{15}H_{22}Cl_3N_6$: C, 41.4; H, 5.1; N, 29.0.

Found: C, 41.4; H, 5.6; N, 28.7.

1,3-Bis-(*p*-ureidophenyl)guanidine (XIII). A solution of 3.5 g. of 1,3-bis-(*p*-aminophenyl)guanidine trihydrochloride in 20 cc. of water was added to a solution of 1.6 g. of potassium cyanate in 15 cc. of water. The temperature rose spontaneously to about 40° and an oil separated. On cooling to 5° and standing the oil crystallized. The product was filtered and washed with cold water; yield 2.4 g. m.p. 193–198° (dec.). The hydrochloride was dissolved in 60 cc. of hot water, the solution was treated with Norit and filtered. Upon cooling the filtrate to 5°, a thin film of oil separated. This was removed by filtration through Norit and Celite. Upon scratching and further cooling the filtrate deposited colorless crystals; m.p. 198–200° (dec.).

Anal. Calc'd for $C_{15}H_{19}ClN_7O_2$: N, 26.9. Found: N, 27.1.

3,3'-Dimethyl-4,4'-diguanidinobiphenyl (XV). A mixture of 14.2 g. of *o*-tolidine dihydrochloride, 6.3 g. of cyanamide, and 100 cc. of ethanol was refluxed one day, the solution was evaporated to dryness *in vacuo*, the residue was dissolved in water, treated with Norit, and filtered. The filtrate was then cooled and made alkaline. A gum separated which crystallized on rubbing. The base was filtered, washed with alkali, then with water, and dried in a desiccator over sulfuric acid; yield 13.5 g., m.p. 219–223° (dec.). The hydrochloride was obtained from the base as a gum.

The picrate formed in aqueous solution. After two recrystallizations from water it decomposed above 270° without melting.

Anal. Calc'd for $C_{23}H_{23}N_{15}O_{14}$: N, 22.3. Found: N, 22.4.

***p*-Guanidinobenzylamine (XVII).** To a boiling solution of 10 g. of *p*-aminobenzylamine dihydrochloride (14) in 10 cc. of water was added, during the course of one hour, a solution of 5 g. of cyanamide in 12 cc. of water. The solution was then refluxed an additional fifteen minutes, cooled to 0–5° and treated with a large excess of 50% alkali. The resulting crys-

talline base was filtered, washed with a little 5 *N* alkali and recrystallized from ethanol-ether; m.p. 172–176°. The base was dissolved in water, neutralized with hydrochloric acid and evaporated to dryness. The resulting dihydrochloride was recrystallized from 90% alcohol and ether; yield 7.5 g., m.p. 250–260° (dec.). After two more recrystallizations the m.p. was 257–260° (dec.).

Anal. Calc'd for $C_8H_{14}Cl_2N_4$: C, 40.5; H, 5.9; N, 23.7.

Found: C, 40.8; H, 7.3; N, 23.4.

The *dipicrate* of *p*-guanidinobenzylamine was formed readily in aqueous solution and after two recrystallizations from water, the m.p. was 242–243° (dec.).

Anal. Calc'd for $C_{20}H_{18}N_{10}O_{14}$: C, 38.6; H, 2.9; N, 22.5.

Found: C, 38.7; H, 3.5; N, 22.3.

p-Aminobenzylguanidine (XVIII). A mixture of 2.4 g. of *p*-aminobenzylamine (free base), 5.0 g. of methylisothiurea sulfate, and 20 cc. of ethanol was refluxed six hours. The white crystalline sulfate was filtered and washed with ethanol; m.p. 195–202° (dec.); yield 5.7 g. The sulfate was dissolved in water and treated with picric acid. The yellow *dipicrate* was filtered and recrystallized three times from water; it decomposes above 197° without melting.

Anal. Calc'd for $C_{20}H_{18}N_{10}O_{14}$: C, 38.6; H, 2.9; N, 22.5.

Found: C, 39.0; H, 3.3; N, 22.4.

p-Guanidinobenzylguanidine (XVI). Two and four-tenths grams of *p*-guanidinobenzylamine dihydrochloride was dissolved in 10.4 cc. of 1.06 *N* sodium hydroxide. The solution was brought to reflux and treated, during two hours, with 2.8 cc. of a 23% aqueous cyanamide solution.

Excess aqueous picric acid was added and the yellow *dipicrate* was filtered and recrystallized four times from water; yield 2.5 g., m.p. 250–253° (dec.). A mixture of the latter and the *dipicrate* of *p*-guanidinobenzylamine [m.p. 242–243° (dec.)] melted at 230–234° (dec.).

Anal. Calc'd for $C_{21}H_{20}N_{12}O_{14}$: C, 38.0; H, 3.0; N, 25.3.

Found: C, 38.7; H, 3.3; N, 25.4.

p-Biguanidobenzylamine dihydrochloride (XXII). A mixture of 9.8 g. of *p*-aminobenzylamine dihydrochloride, 8.4 g. of dicyandiamide, and 20 cc. of water was refluxed two hours and cooled to 5°. The white solid was filtered, washed with ethanol, and recrystallized three times from 85% ethanol-ether; yield 8 g. The crystals decomposed above 250° without melting.

Anal. Calc'd for $C_9H_{12}Cl_2N_6$: C, 33.8; H, 5.7; N, 30.1.

Found: C, 38.6; H, 6.1; N, 29.6.

p-Phenylenedibiguanide (XXIII). An intimate mixture of 2.7 g. of *p*-phenylenediamine dihydrochloride and 2.5 g. of dicyandiamide was heated in a tube at 150–160° (inner temperature) for one hour. The mixture fused partly. The mass was cooled, dissolved in water, decolorized with charcoal, cooled to 5°, and made alkaline with 5 *N* sodium hydroxide. The free base separated in the form of sparkling crystals which were filtered and washed with cold water; yield 2.7 g., m.p. 217–218° (dec.). After two recrystallizations from water, the m.p. was 218–219° (dec.).

Anal. Calc'd for $C_{10}H_{16}N_{10} \cdot H_2O$: C, 40.8; H, 6.1; N, 47.6.

Found: C, 41.0; H, 6.6; N, 46.6.

Acidification of the base with hydrochloric acid gives a tetra-hydrochloride, which crystallizes from the strongly acid solution. The salt was dissolved in water and hydro-

chloric acid was again added. The partially purified salt was then recrystallized from dilute alcohol and ether; m.p. 270-278° (dec.).

Anal. Calc'd for $C_{10}H_{20}Cl_4N_{10}$: C, 28.5; H, 4.7; N, 33.2; Cl, 33.7.

Found: C, 29.1; H, 5.2; N, 33.9; Cl, 32.0.

2-Chloro-1,4-phenylenedibiguanide (XXIV). A mixture of 4.3 g. of 2-chloro-1,4-phenylenediamine dihydrochloride, 3.4 g. of dicyandiamide, and 8 cc. of water was refluxed for two hours, the solution was evaporated to dryness, and the gummy residue was triturated with warm ethanol. The resulting crystals (4.2 g.) of the hydrochloride were filtered and recrystallized from 85% ethanol-water; m.p. 240-243° (dec.). The hydrochloride was converted to the base with 50% alkali and the resulting white crystalline base was recrystallized twice from water; m.p. 208-210° (dec.).

Anal. Calc'd for $C_{10}H_{18}ClN_{10}$: C, 38.7; H, 4.8; N, 45.2.

Found: C, 38.1; H, 4.9; N, 45.3.

SUMMARY

The preparation of a number of guanidine and biguanide derivatives related to *p*-phenylenediguanidine has been described; these were tested for trypanocidal activity.

PEARL RIVER, NEW YORK

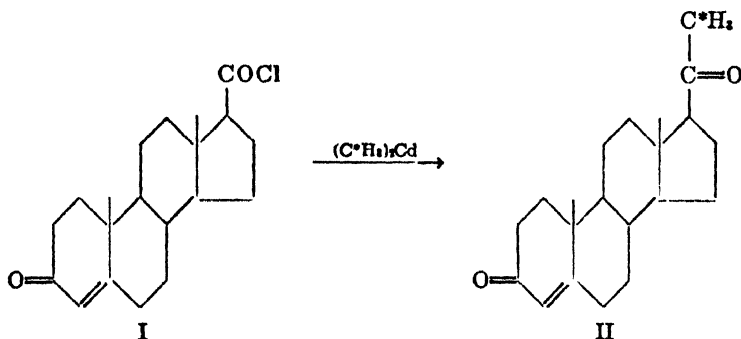
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THE SYNTHESIS OF PROGESTERONE-21-C¹⁴BYRON RIEGEL AND FRANKLIN S. PROUT¹*Received August 16, 1948*

As a part of a program to study the intermediary metabolism of steroids, radioprogesterone (II) has been prepared. This labeled hormone was made by the alkylation of 3-keto-4-etiochenoyl chloride with radioactive dimethylcadmium.

Several procedures for the labeling of progesterone in the side chain were examined critically. The method of Butenandt and Schmidt-Thomé (1) beginning with the cyanhydrin reaction on β -dehydroandrosterone acetate was investigated extensively. However, we failed to achieve consistently the high yields obtained by these authors. Efforts to prepare 17-chloro(or bromo)-3 β -acetoxy-5-androstene by chlorination of 3 β -acetoxy-5-androsten-17-ol (2) or degradation of silver 3 β -acetoxy-5-etiochenolate with bromine (3) gave rearranged products. Carbonation (4) of these halides would give 3 β -acetoxy-5-etiochenic acid-20-C¹⁴ which could then be alkylated with dimethylcadmium (5).



Our synthesis utilizes 3-keto-4-etiochenoyl chloride (I), whose preparation has recently been described by Wilds and Shunk (6). While the alkylation of this 3-keto acid chloride with dimethylcadmium gives somewhat smaller yield than the alkylation of 3 β -acetoxy-5-etiochenoyl chloride (5), avoidance of two steps after introduction of the radiocarbon justifies the one-step procedure.

Isotopic methanol was converted to methyl bromide by an adaptation of Tolbert's procedure (7) for the preparation of methyl iodide. Using a simplified vacuum line, the methanol was quantitatively converted to methyl bromide when allowed to stand with phosphorus tribromide for four hours. The methyl bromide was purified by distilling through a column packed with both acid and alkali absorbents. The first part of the packing was porcelain chips soaked with concentrated sulfuric acid, and the second part was pellets of sodium hydroxide.

¹ American Cancer Society Research Associate, 1947-1948. Present address: Department of Chemistry, DePaul University, Chicago, Illinois.

Portions of the methyl bromide were transferred using vacuum technique to a flask, containing the ether and magnesium, cooled with liquid air. After each addition, the flask was shut off from the system and the reaction was allowed to take place at room temperature. The Grignard reagent was prepared in about an 80% yield. The methylmagnesium bromide was converted to dimethylcadmium by the usual procedure of adding anhydrous cadmium chloride. The acid chloride in dry benzene was then added to the ether solution.

The reaction mixture was worked up in the usual way and the product was chromatographed on activated alumina, molecularly distilled, and finally crystallized from acetone-hexane. This gave a 29% yield of progesterone-21-C¹⁴ based on the radiomethanol employed. The labeled progesterone melted at 122.1–125.6°, gave a specific rotation of +191° and a specific activity of 2.5×10^4 counts/sec./mg.

Acknowledgment. The authors wish to express their appreciation for a grant from the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council for the support of this work. We wish to thank Dr. Percy L. Julian and Dr. Wayne Cole of the Soya Products Division of the Glidden Company for their technical advice and for permission to use steroid intermediates furnished for the Glidden Fellowship. We also wish to thank Dr. Austin M. Brues and Miss Agnes Naranjo of the Argonne National Laboratory for making the activity counts.

Note added in proof: Dr. T. F. Gallagher has informed us that Dr. H. B. MacPhillamy of the Ciba Pharmaceutical Products, Inc. has carried out essentially the same synthesis of radioprogestosterone at the Sloan-Kettering Institute for Cancer Research.

EXPERIMENTAL

Radiomethyl bromide. The conversion of methanol to methylmagnesium bromide was accomplished in a small manifold equipped with three outlet tubes fitted with appropriate standard taper joints, a storage bulb, a closed-end manometer of about 100 mm. length and a connection to a high vacuum line. All outlets were equipped with stopcocks. The volumes of the manifold (288 cc.) and storage bulb (217 cc.) were known and utilized to determine the quantities of gas manometrically.

Two portions of methanol, 0.06 cc. of ordinary dry methanol and 0.59 mmol. of radioactive methanol,² were attached to the manifold and frozen in liquid air and the system was evacuated to 0.5 μ . The isotopic methanol was transferred at low pressure to the storage bulb and then allowed to evolve into the manifold-storage bulb system to register 18 mm. pressure, equivalent to 0.59 mmol.³ Similarly, the ordinary methanol was transferred, and when it was allowed to expand into the manifold-storage bulb system, the pressure recorded was 65 mm. or equivalent to 2.1 mmol. of methanol.

After the methanol was returned to the storage bulb, a 45-cc. reaction bulb fitted with a stopcock and joint and charged with 0.23 cc. of phosphorus tribromide was attached to the

² The radioactive methanol containing 1 mc. in 0.59 mmol. was obtained from the United States Atomic Energy Commission, Oak Ridge, Tennessee.

³ In the 505-cc. manifold-storage bulb system at ca. 33° the millimoles of gas were calculated as follows: $\frac{303}{273} \times \frac{500}{22.4} \times \frac{18}{760} = 0.59$ mmol.

manifold, cooled in liquid air and evacuated to 3 μ . The methanol was distilled into the reaction bulb and the stopcock was shut. The bulb was removed from the line and was allowed to stand at room temperature (ca. 30°) for four hours. This bulb was then attached to the manifold with a drying tube, packed so that the evolving methyl bromide passed in order through porcelain chips saturated with concentrated sulfuric acid and sodium hydroxide pellets. After evacuation of the system to 3 μ , the methyl bromide was allowed to evolve slowly, eventually heating the bromide reaction mixture up to 0° and condensing the methyl bromide in the storage bulb with liquid air. On allowing the methyl bromide to expand into the manifold-storage bulb system, the pressure was 66 mm., indicating a quantitative yield of bromide.

Progesterone-21-C¹⁴ (II). A two-neck, 50-cc. flask containing 60 mg. (2.5 mmol.) of magnesium and a small magnetic stirrer were attached to one of the outlets. Eleven cubic centimeters of dry ether was added and a drop of 0.1 *M* methylmagnesium bromide solution to assure dryness. The ether solution was frozen in liquid air and the system was evacuated to 0.5 μ . Twenty-nine per cent of the methyl bromide was frozen in this flask, the flask shut off from the manifold and the reaction mixture was warmed to room temperature. The reaction was stirred for thirty minutes. The remainder of the bromide was added in three additional portions (41%, 20%, and 9%) in the same manner. In one run the Grignard reagent was filtered and shown by titration (8) to have been formed in an 80% yield.

At this point nitrogen was admitted into the system and the reaction was continued at atmospheric pressure in a nitrogen atmosphere. Freshly dried cadmium chloride (0.26 g., 1.4 mmol.) was added and the mixture was stirred for two hours at room temperature. The acid chloride (I) was prepared from 595 mg. of sodium 3-keto-4-etiocholenate by the method of Wilds and Shunk (6) employing oxalyl chloride. The 3-keto-4-etiocholenoyl chloride (I) dissolved in 10 cc. of benzene was added to the dimethylcadmium solution. The resulting gummy mixture was stirred for ten hours at room temperature and heated under reflux for three hours more. Then 5 cc. of 1:24 sulfuric acid was added and boiling was continued for an hour to effect decomposition of the complex and to rearrange any isoprogesterone which might have been formed (9). The aqueous phase was separated and extracted with two portions of benzene. After washing successively with water, 5% potassium carbonate solution, water, and saturated sodium chloride solution, the extracts were dried with sodium sulfate; and the solvent was removed to give 375 mg. of oil. The carbonate washes were acidified to give 212 mg. of acid; m.p. 175–195°.

The crude oil was chromatographed on 10 g. of acid-washed alumina (80–200 mesh, activated at 250°). After developing with 50 cc. of benzene the progesterone was eluted with 50 cc. of 1:4 ethyl acetate-benzene to furnish 290 mg. of partly purified progesterone. Molecular distillation of this product at 0.5 μ . pressure gave three fractions: A, 214 mg. at 120–155°; B, 31 mg. at 155–190° and C, 20 mg. at 190–200°. Recrystallization of A from 3 cc. hexane-0.5 cc. acetone furnished 147 mg. of progesterone as heavy prisms, probably in the β -form: m.p. 122.1–125.6°; $[\alpha]_D^{25} + 191^\circ$ (6.7 mg. made up to 2 cc. with 95% ethanol, α_D^{25} 1.28°, 1, 2 dm.). The literature values are: m.p. 121° (β -form); 128.5° (α -form); $[\alpha]_D^{25} + 191.5^\circ$ (absolute ethanol) (10). Further work-up on fractions B and C and the mother liquors gave an additional 46 mg. (total yield, 193 mg., 29 2%, based on methanol used).

In preliminary runs the yield of progesterone (based on methanol) was found to be 25% with a 1:1 ratio of methanol to acid chloride and 7.6% with a ratio 5:1. In this last case the yield was 43%, based on the acid chloride. In comparable runs on the alkylation 3- β -acetoxy-5-etiocholenoyl chloride (5), we obtained 31% yield of pregnenolone acetate using a 1:1 ratio and a 17% yield using a 4:1 ratio of methanol to acid chloride.

SUMMARY

The preparation of isotopic methyl bromide on a millimole scale has been described. This radioactive methyl bromide has been converted to dimethyl-

cadmium and used to alkylate 3-keto-4-etiocholenoyl chloride to furnish progesterone-21-C¹⁴.

EVANSTON, ILLINOIS

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ERRATA

G. Bryant Bachman and D. E. Welton, "Oximes of Dialkylaminobutanediones", *J. Org. Chem.*, **12**, 222 (1947).

Formula VI (in equation) $\text{CH}_3\text{C}(=\text{NOH})\text{C}(=\text{NOH})\text{CH}_3$ should read $\text{CH}_3\text{C}(=\text{NOH})\text{C}(=\text{NOH})\text{CH}_2\text{NR}_2 + \text{H}_2\text{O}$

L. Haskelberg, "Derivatives of 6-Nitro- and 6-Amino-quinoline", *J. Org. Chem.*, **12**, 434 (1947).

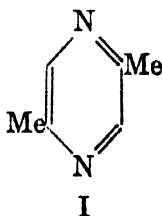
In this paper, the cyclization of the crude reaction product from 6-amino-quinoline and ethyl acetoacetate was described to give 2-hydroxy-4-methyl-5,6,3',2'-pyridoquinoline (I). Dr. W. O. Kermack has drawn our attention to the fact that the synthetic method applied is expected to lead to 4-hydroxy-2-methyl-5,6,3',2'-pyridoquinoline (II) [see Kermack and Weatherhead, *J. Chem. Soc.*, 1164 (1940)] rather than to (I). In comparing our product with an authentic specimen of (I) (m.p. 330° after shrinking at 325°), he observed a depression of the melting point of the mixture to 300° (beginning of the melting). The substance in question has, therefore, formula (II). Dr. Kermack's advice and assistance is gratefully acknowledged.

Lyndon Small, Lewis J. Sargent, and James A. Bralley, "The Phenylidihydrothebaines", *J. Org. Chem.*, **12**, 842 (1947).

Table I, column three, (-)Hexahydrophenyltetrahydrothebaimine (XXXI), $(\alpha)_D - 10.0$ should read $(\alpha)_D + 10.0$.

Frederick George Mann and James Watson, *J. Org. Chem.*, **13**, 502 (1948).

Page 502, Formula I



should be



Page 507, line 7 from bottom, formula $\text{C}_6\text{H}_5\text{N}\overset{\downarrow}{\text{O}}:\text{NC}_6\text{H}_5$ should read
 $\text{C}_6\text{H}_5\text{N}:\text{NC}_6\text{H}_5$
 \downarrow
 O

Page 507, line 5 from bottom, formula $\text{C}_6\text{H}_5\text{N}\overset{\downarrow}{\text{O}}:\overset{\downarrow}{\text{O}}\text{NC}_6\text{H}_5$ should read
 $\text{C}_6\text{H}_5\text{N}:\text{NC}_6\text{H}_5$
 $\downarrow \quad \downarrow$
 $\text{O} \quad \text{O}$

Electronic Interpretation of Organic Chemistry. I. The Role of Solvent in Determining Reaction Rate. Santi R. Palit, *J. Org. Chem.*, **12**, 758 (1947). Add to last sentence "be difficult to predict. However, as we have clearly illustrated our concept by the above typical examples, we shall not extend the same to the other rather limited data available."

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